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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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Abstract

Background: Observational studies of people with chronic obstructive pulmonary disease using beta-blockers for cardiovascular disease indicate that beta-blocker use is associated with reduced risk of chronic obstructive pulmonary disease exacerbation. However, at the time this study was initiated, there had been no randomised controlled trials confirming or refuting this.

Objective(s): To determine the clinical and cost-effectiveness of adding bisoprolol (maximal dose 5 mg once daily) to usual chronic obstructive pulmonary disease therapies in patients with chronic obstructive pulmonary disease at high risk of exacerbation.

Design: A multicentre, pragmatic, double-blind, randomised, placebo-controlled clinical trial.

Setting: Seventy-six United Kingdom primary and secondary care sites.

Participants: People aged ≥ 40 years with a diagnosis of at least moderately severe chronic obstructive pulmonary disease with a history of at least two exacerbations in the previous year.

Interventions: Participants were randomised (1 : 1) to receive either bisoprolol or placebo for 1 year. During a 4- to 7-week titration period, the maximum tolerated dose was established (1.25 mg, 2.5 mg, 3.75 mg, 5 mg once daily).

Primary outcome: A number of participant-reported exacerbations during the 1-year treatment period.

Results: In total, 519 participants were recruited and randomised. Four post-randomisation exclusions left 259 in the bisoprolol group and 256 in the placebo group. Treatment groups were balanced at baseline: mean (standard deviation) age 68 (7.9) years; 53% men; mean (standard deviation) pack year smoking history 45 (25.2); mean (standard deviation) 3.5 (1.9) exacerbations in previous year. Primary outcome data were available for 99.8% of participants (bisoprolol 259, placebo 255). The mean (standard deviation) number of exacerbations was 2.03 (1.91) in the bisoprolol group and 2.01 (1.75) in the placebo group (adjusted incidence rate ratio 0.97, 95% confidence interval 0.84 to 1.13), $p = 0.72$. The number of participants with serious adverse events was similar between the two groups (bisoprolol 37, placebo 36). The total number of adverse reactions was also similar between the two groups. As expected, bisoprolol was associated with a higher proportion of vascular adverse reactions (e.g. hypotension, cold peripheries) than placebo, but was not associated with an excess of other adverse reactions, including those classified as respiratory. Adding bisoprolol resulted in a statistically insignificant trend towards higher costs (£636, 95% confidence interval £118 to £1391) and fewer quality-adjusted life-years (0.035, 95% confidence interval 0.059 to 0.010) compared to placebo.

Limitations: The study findings should be interpreted with caution as the target sample size of 1574 was not achieved because the funder considered the study to be unviable in the COVID-19 pandemic clinical research environment. Although 28% of participants did not initiate bisoprolol/placebo (1.6%) or ceased during the treatment period (26.2%), this is consistent with similar trials in the United Kingdom.

Conclusions: In this underpowered study, the addition of bisoprolol to usual chronic obstructive pulmonary disease treatment did not reduce the likelihood of exacerbations, and bisoprolol cannot be recommended as a treatment for chronic obstructive pulmonary disease.

Future work: To incorporate definitive statements into appropriate clinical guidelines about the safety of bisoprolol for cardiovascular indications in people with chronic obstructive pulmonary disease.

Trial registration: This trial is registered as ISRCTN10497306.

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Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/TNDG8641).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

ACOS	asthma, COPD overlap syndrome
AR	adverse reaction
ATS	American Thoracic Society
BDI	Baseline Dyspnoea Index
BICS	bisoprolol in COPD study
BLF	British Lung Foundation
BLOCK COPD	Beta-Blockers for the Prevention of Acute Exacerbations of COPD
BMI	body mass index
BNF	*British National Formulary*
b.p.m.	beats per minute
CAT	COPD assessment test
CEAC	cost-effectiveness acceptability curve
CHaRT	Centre for Healthcare Randomised Trials
CHSS	Chest Heart & Stroke Scotland
COPD	chronic obstructive pulmonary disease
CRN	Clinical Research Network
CSRI	Client Service Receipt Inventory
CT	computed tomography
DALY	disability-adjusted life-year
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECLIPSE	Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints
EQ-5D-5L	EuroQoL-5 Dimensions, five-level version
ERS	European Respiratory Society
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	general practitioner
HARQ	Hull Airway Reflux Questionnaire
ICS	inhaled corticosteroid
ITT	intention to treat
LABA	long-acting beta2 agonist
LAMA	long-acting muscarinic antagonist
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
NICE	National Institute for Health and Care Excellence
NIHR HTA	National Institute for Health and Care Research Health Technology Assessment
PACE	Preventing Adverse Cardiac Events
PIC	Participant Identification Centre
PIL	participant information leaflet
PPE	personal protective equipment
PPI	public and patient involvement
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life-year
RCT	randomised controlled trial
REC	Research Ethics Committee
SABA	short-acting beta2 agonist
SAE	serious adverse event
SAR	serious adverse reaction
SmPC	summary of product characteristics
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reaction
SVC	slow vital capacity
TDI	Transition Dyspnoea Index
TSC	Trial Steering Committee
TWICS	theophylline with inhaled corticosteroids
VAS	visual analogue scale

Plain language summary

Chronic obstructive pulmonary disease is a lung disease causing shortness of breath. It has no cure and is a leading cause of death. It affects about 1.2 million people in the United Kingdom and costs the National Health Service around £1.9B each year. People with chronic obstructive pulmonary disease often have symptom 'flare-ups' (exacerbations) that usually need emergency treatment and impact the quality of life.

Bisoprolol is usually used to treat cardiovascular diseases such as high blood pressure and heart failure. In observational research, people with chronic obstructive pulmonary disease who take beta-blockers have been reported to have a reduced chance of having exacerbations. The bisoprolol in chronic obstructive pulmonary disease study tested whether adding bisoprolol to usual chronic obstructive pulmonary disease treatments reduced exacerbations in people with chronic obstructive pulmonary disease.

A total of 515 people with chronic obstructive pulmonary disease from 76 hospitals and general practitioner practices across the United Kingdom took part in the bisoprolol in chronic obstructive pulmonary disease study. They were randomly divided into two groups: one group (259 people) took bisoprolol pills every day and the other group (256 people) took dummy pills. People did not know which group they were in. We followed people for up to 12 months and counted how many exacerbations they had. In both groups, people had on average two exacerbations in 12 months. There was no difference between the groups – so bisoprolol did not reduce the number of exacerbations that people had. The bisoprolol group did not have any more serious adverse events or respiratory side effects than the placebo group.

The COVID-19 pandemic had a major impact on the bisoprolol in chronic obstructive pulmonary disease study: we planned to recruit 1574 patients but were only able to recruit 515; so, the results have to be interpreted with some caution. Nevertheless, the results from the bisoprolol in chronic obstructive pulmonary disease study are important. Although bisoprolol did not reduce exacerbations and cannot be recommended as a treatment for chronic obstructive pulmonary disease, bisoprolol was safe for patients with chronic obstructive pulmonary disease. This important finding means that bisoprolol can be used to treat cardiovascular diseases in patients who have chronic obstructive pulmonary disease.

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.

Funding

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Chapter 1 Introduction

The 2023 Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy document defines chronic obstructive pulmonary disease (COPD) as 'a heterogenous lung condition characterised by chronic respiratory symptoms (dyspnoea, cough, sputum production, exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive airflow obstruction'.[1] COPD is predominantly caused by the inhalation of toxic particles and gases,[2] most notably from tobacco smoking[3,4] but indoor and outdoor air pollution and occupational exposure to dust, vapours and fumes can be significant contributory factors.[5,6] COPD prevalence and outcomes are very strongly associated with social deprivation and poverty.[7–10] People with COPD typically present with progressively worsening breathlessness on exertion and a productive cough, and COPD is usually diagnosed from the age of 40 onwards and prevalence increases with age.[11] The progressive airflow limitation of COPD is associated with increasing disability, work absence, long-term morbidity, common physical and psychological comorbidities, and premature mortality. People with COPD are more likely to have associated comorbidities,[12] including ischaemic heart disease,[13] hypertension,[14] heart failure, diabetes,[15] metabolic syndrome, osteoporosis,[16] depression[17] and lung cancer,[18] which increase morbidity, worsen prognosis and complicate its management.[19] Unrecognised heart failure has been reported in up to 14% of COPD patients.[20,21] In the UK, it has been reported that 26% of people with COPD have ≥ 2 comorbidities.[22]

Acute deteriorations in symptoms known as exacerbations are an important clinical feature of COPD and are the primary outcome of the current study. Exacerbations are usually precipitated by viral/bacterial infection and/or air pollution and are characterised by increasing breathlessness, and/or cough, sputum expectoration and malaise. Exacerbations are associated with accelerated rate of lung function decline,[23] reduced physical activity,[24] reduced quality of life,[25] increased mortality,[26] increased risk of comorbidities[27] and increased direct and indirect costs.[28] The observational Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study identified a frequent exacerbator phenotype defined as ≥ 2 exacerbations in a year which affects about 25% of COPD patients.[29] Patients with this phenotype have an 84% chance of at least one exacerbation in the subsequent year; moreover, this frequent exacerbator phenotype is stable for at least 3 years and can be reliably identified by patient recall.[29] Frequent exacerbators incur a disproportionate amount of the annual NHS spend on COPD.

The burden of chronic obstructive pulmonary disease on individuals and the National Health Service

Globally, an estimated 391 million people have COPD, 80% of whom (315 million) live in low-middle income countries.[2] In 2019, an estimated 3.2 million people died of COPD globally, making COPD the third leading cause of death worldwide.[30,31] In high-income countries, COPD is the fifth leading cause of death, whereas in low-middle income countries, COPD is the third/fourth leading cause of death. In addition to being a leading cause of death, COPD is a leading cause of disease burden as quantified as disability-adjusted life-years (DALYs). COPD is the sixth leading cause of disease burden globally for all age groups; for the 50–74 year age group, COPD is the fourth leading cause of DALYs; and for ≥ 75-year age group, COPD is the third leading cause of DALYs.[32]

In the UK, COPD is a major personal and public health burden.[33] In 2015, an estimated 1.2 million people in the UK were living with a diagnosis of COPD (4.5% of the > 40-year population) and this appears to be increasing.[33] The prevalence of COPD in the UK is highest in the Northeast, the Northwest and Scotland. The UK has the 12th highest recorded deaths from COPD in the world, with an age-standardised mortality rate of 210 deaths per million; COPD is the third leading cause of death in the UK with about 35,000 people dying of COPD in 2019.[34] More than 80% of COPD patients, irrespective of severity, report a reduced quality of life.[35,36] The Continuing to Confront COPD International Patient Survey reported that 53% of people with COPD in the UK are of working age, 52% of whom are unable to work because of their COPD.[22] It has been estimated that the total economic cost of each person with COPD to the UK is $18,803, 83% of which ($15,579) are indirect costs related to premature retirement and reduced productivity.[22] COPD costs the NHS £1.9B/year ($2.4B);[37] for each patient with COPD in 2012–3, average annual NHS direct costs were $3224, with 26% of this being accounted for by general practitioner (GP) visits, 26% by

specialist visits, 20% by inpatient hospitalisations exacerbations and 10% due to drug costs.[22] Most (81%) COPD care is usually provided by GPs, and each patient with COPD has a mean [standard deviation (SD)] 8.3 (11.9) COPD-related visits to GPs each year.[22] COPD is the second leading cause of emergency admission to hospital in the UK and is one of the costliest inpatient conditions treated by the NHS.[38] In 2018–9, there were 137,000 hospital admissions for exacerbation of COPD, with an average length of stay of 6 days, accounting for 660,000 bed-days.[39] In the UK, 15% of COPD care is usually provided by a specialist, and 15% of people with COPD reported that they have been admitted once to hospital in the past year.[22] Over 30% of patients admitted to hospital with an exacerbation of COPD are re-admitted within 30 days, and an average of 12% of COPD patients die in the year following admission to hospital with a severe exacerbation.[26]

Despite advances in management, there is still an unmet need for improved pharmacological treatment of COPD, particularly in the prevention of exacerbations; the study presented here addressed this issue by testing whether administering the beta-blocker bisoprolol to people with COPD reduced the rate of COPD exacerbation.

Rationale for a study of beta-blockers in people with chronic obstructive pulmonary disease

Beta-adrenoceptor-blocking drugs (beta-blockers) block the beta-adrenoceptors in the heart, peripheral vasculature, bronchi, pancreas and liver. It is well-established that beta-blockers reduce morbidity and mortality in people with ischaemic heart disease and heart failure, with beta-blocker use being a guideline recommendation for people who have suffered a myocardial infarction or have heart failure with reduced ejection fraction.[40,41] At the time the current study was being developed, there was a substantial body of evidence from observational studies and cardiovascular trials that beta-blockers were associated with reduced mortality and exacerbations in people with COPD.[42–48] In 2014, a systematic review of observational studies and cardiovascular trials of beta-blockers in people with COPD identified 15 studies with a total 121,956 COPD patients followed up for between 1 and 7 years.[42] Meta-analysis demonstrated that beta-blocker use in people with COPD was associated with 28% [95% confidence interval (CI) 17 to 37] reduced mortality and 37% (95% CI 29 to 43) reduced exacerbations. The systematic review identified the need for long-term trials to assess the safety and efficacy of beta-blockers in patients with COPD and to clarify whether beta-blockers are beneficial to COPD patients without cardiovascular comorbidities.[42]

One of the issues complicating studies of beta-blockers in COPD is that exacerbations of COPD and heart failure share common symptomatic presentation, and beta-blockers have a proven benefit in heart failure. It is possible that misclassification of heart failure exacerbations as COPD exacerbations may erroneously result in beta-blockers being associated with reduced COPD exacerbations. However, at the time the current study was being developed, there was evidence that beta-blocker use in people with COPD without known cardiovascular disease was associated with a reduced risk of acute exacerbations of COPD and that any beneficial effect of cardioactive drugs on COPD exacerbations seemed to be specific to beta-blockers. In a Dutch observational cohort study, beta-blocker use in people with COPD without known cardiovascular disease was associated with reduced likelihood of COPD exacerbation [hazard ratio (HR) 0.66, 95% CI 0.52 to −0.86].[43] In a further observational study, beta-blocker use was associated with a reduced risk of exacerbation in people with COPD with computed tomography (CT) evidence of coronary artery disease [incidence rate ratio (IRR) 0.67, 95% CI 0.48 to 0.93] and also in people with COPD without coronary artery disease on CT imaging (IRR 0.76, 95% CI 0.58 to 0.99).[44] This study also noted that the beneficial effect of beta-blockers was evident in patients requiring long-term oxygen therapy and was class-specific, with the use of other cardioactive drugs used to treat heart disease (e.g. calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers) having no demonstrable effect on the risk of COPD exacerbation.[44]

The justification for the bisoprolol in COPD study (BICS) was based on the findings of systematic reviews of observational studies and cardiovascular trials that beta-blocker use in people with COPD reduced their risk of exacerbations; moreover, the beneficial association with exacerbations extended to people with COPD without cardiovascular disease and appeared to be class-specific. However, the positive results of these observational studies and cardiovascular trials needed to be treated with caution, and a pragmatic, prospective, double-blind, randomised trial was justified.

Safety of beta-blockers in people with chronic obstructive pulmonary disease

One of the issues surrounding the use of beta-blockers in people with COPD is that of safety because of clinical concerns about adverse effects on respiratory function and interference with medications used to treat COPD. The beta-adrenergic system contains beta1- and beta2-adrenoreceptors; beta1-adrenoreceptors are predominantly found in the heart, whereas beta2-adrenoreceptors are more ubiquitous being predominantly found in the heart and lungs but also in skeletal muscle and peripheral blood vessels. Beta-blockers that antagonise the effects of beta2-agonists could have adverse respiratory effects; indeed for asthma, a condition with reversible airflow limitation, beta-blockers are contraindicated.[49] Beta1-selective blockers such as bisoprolol have 13.5–19.6 times more affinity for beta1-adrenoreceptors than for beta2-adrenoreceptors[50,51] and should not cause bronchoconstriction. Clinical evidence is supportive of bisoprolol being safe in COPD, and beta1-selective blocker use in COPD patients with heart failure is a guideline recommendation because it is considered safe.[41] Despite guideline recommendations, the use of beta-blockers in people with COPD with cardiovascular disease remains suboptimal because of unfounded concerns about possible adverse effects of beta-blockade on airway function.[45,52–56] The evidence at the time BICS was being developed was that the use of beta-blockers in people with COPD would be safe. A systematic review with meta-analysis of randomised controlled trials (RCTs) investigating the effects of beta1-selective blockers on lung function [forced expiratory volume in 1 second (FEV1)] and respiratory symptoms in people with COPD reported that administration of beta1-selective blockers to people with COPD was not associated with any significant change in FEV_1, any increase in respiratory symptoms or any change in response to inhaled beta2-agonist treatment.[57]

In summary, multiple observational studies and cardiovascular trials indicate that beta1-selective blockers are potentially beneficial in reducing exacerbations in people with COPD, including those without cardiovascular disease. For the majority of people with COPD, there is no indication for beta-blocker use for cardiovascular disease. Despite guideline recommendations, beta-blockers continue to be underutilised in people with COPD, because of unfounded safety concerns. A prospective, randomised, placebo-controlled trial was deemed appropriate to investigate whether beta-blockers are beneficial in COPD and to address unsubstantiated safety concerns in people with COPD. BICS was a pragmatic effectiveness trial of once daily bisoprolol (a beta1-selective blocker) versus placebo in people with COPD at high risk of acute exacerbation to determine primarily clinical and cost-effectiveness in preventing exacerbations.

Hypothesis

The hypothesis being tested was that the repurposing of a well-known and inexpensive drug bisoprolol added to usual COPD treatment reduced the risk of COPD exacerbation requiring treatment with antibiotics and/or oral corticosteroids during the year of treatment, delivered quality of life improvements, and was safe and cost-effective.

Objectives

Primary objective

The primary objective was to determine the clinical (in terms of number of exacerbations requiring change in management) 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 a previous year.

Secondary objectives

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 event (MACEs).
- Lung function.

- Changes in breathlessness during treatment.
- All-cause, respiratory and cardiac 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-year (QALY).
- Costs to the NHS and patients and lifetime cost-effectiveness based on extrapolation modelling.
- Modelled lifetime incremental cost per QALY.

End points/outcomes

Primary end point/outcome

The primary outcome measure was the total number of exacerbations of COPD necessitating changes in management (minimum management change – use of oral corticosteroids and/or antibiotics) during the 1-year treatment period, as reported by the participant.

The primary economic outcome measure was the cost per QALY gained during the 1-year treatment period.

Secondary end points/outcomes

- Total number of COPD exacerbations requiring hospital admission*.
- Time to first exacerbation of COPD.
- Total number of emergency hospital admissions (all causes)*.
- Total number of MACEs (defined by cardiovascular death, hospitalisation for myocardial infarction, heart failure or stroke), percutaneous coronary intervention or coronary artery bypass grafting*.
- Lung function [FEV_1, forced vital capacity (FVC)] post bronchodilator using spirometry performed to American Thoracic Society/European Respiratory Society (ATS/ERS) standards.
- Breathlessness using Baseline and Transition Dyspnoea Indices (BDI and TDI).
- All-cause, respiratory and cardiac mortality*.
- SAEs, adverse reactions (ARs).
- Health-related quality of life using EuroQol-5 Dimensions, five-level version (EQ-5D-5L) Index.
- Disease-specific health status using the COPD assessment test (CAT).
- Utilisation of primary or secondary health care for respiratory events*.
- Change in disease-associated symptoms using the Hull Airways Reflux Questionnaire (HARQ) (this was only done at some self-selecting recruitment sites).
- Modelled lifetime incremental cost per QALY.

*The time period was the year of treatment, that is number of events per year of treatment.

Role of the funder

The study was funded by the National Institute for Health Research Health Technology Assessment (NIHR HTA) programme. The NIHR had input into the trial design through peer review of the proposal but did not have a role in data collection, data analysis, data interpretation or the writing of the final report. The corresponding author had access to all the data and was responsible for the decision to submit.

Chapter 2 Methods/design

Trial design

The study protocol has been published in an Open Access journal[58] and is similar to that used for our trial of low-dose theophylline in COPD.[59,60] Some material has been reproduced from Devereux *et al.*[59] This is an Open Access article distributed in accordance with the terms of the CreativeCommons Attribution License (CC BY 4.0), which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The text below includes minor additions and formatting changes to the original text.

Bisoprolol in COPD study was a pragmatic, double-blind, randomised, placebo-controlled, UK multicentre clinical trial comparing the addition of bisoprolol or placebo for 1 year to current COPD therapy in patients with COPD with a self-reported history of two or more exacerbations of COPD in a previous year treated with oral corticosteroids and/or antibiotics. This study followed the Consolidated Standards of Reporting Trials guidelines.

Many aspects of the methods used to conduct the BICS were affected by the COVID-19 pandemic, and these are described below.

The aim of the study was to recruit 1574 participants, with at least 50% being recruited in primary care. The trial was approved by Scotland A Research Ethics Committee (REC) (ref 18/SS/0033) and the Medicines and Healthcare products Regulatory Agency (MHRA) (EudraCT 2017-002779-24, CTA 21583/0222/001). The study was registered on 16 August 2018: ISRCTN10497306. All participants provided written informed consent, and this included consent to inform the participant's GP of involvement and consent to pass on participant's name and address to a third-party courier who delivered the study medication to the participant's home.

Figure 1 provides a schematic representation of study design.

Figure 2 provides a schematic representation of the study schedule. Study assessments were conducted for all participants at recruitment/baseline, 26, and 52 weeks. Up to an additional four dose-titration assessments were carried out at approximately 1, 2, 3 and 4 weeks, with the actual number determined by tolerability of study medication and the dose-titration algorithm (see below). Where face-to-face study assessments (e.g. during COVID-19) were not possible, these were conducted by telephone or video calls.

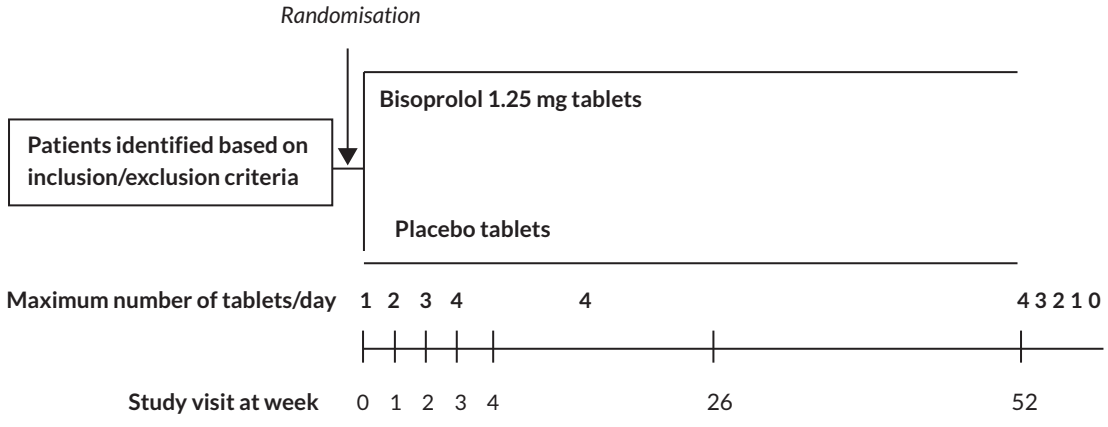

FIGURE 1 Study design.

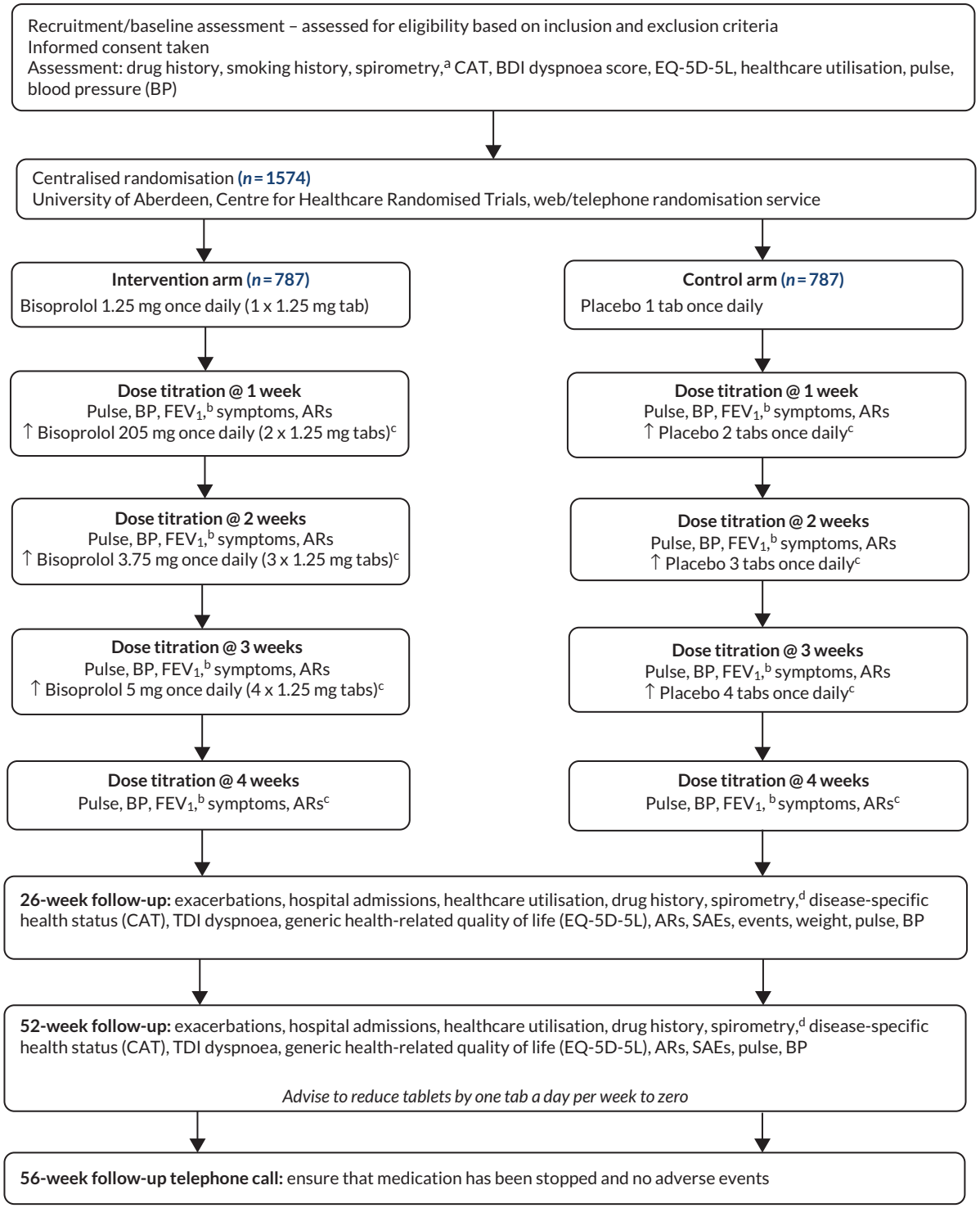

FIGURE 2 Summary of study schedule. a, During the COVID-19 pandemic, historical spirometry results were used. b, During the COVID-19 pandemic, the titration algorithm replaced FEV_1 with patient-reported breathlessness. c, Further details regarding titration are provided later in this chapter and *Figure 3*. d, During the COVID-19 pandemic, 26- and 52-week follow-up were done by telephone or video call and did not include spirometry.

Participants

Inclusion criteria

The participants in BICS were people with COPD likely to exacerbate during the 52-week treatment period as evidenced by two or more exacerbations of COPD in the previous year treated with oral corticosteroids and/or antibiotics. Participants had to meet all the following inclusion criteria that are typical of studies in people with COPD with exacerbations as the primary end point:

- Aged ≥ 40 years.
- A smoking history of at least 10 pack years [(average number of cigarettes/day × years smoked)/20].
- An established predominant diagnosis of COPD [National Institute for Health and Care Excellence (NICE) Guideline definition: post bronchodilator FEV_1 < 80% predicted, FEV_1/FVC < 0.7] receiving treatment as per local guidelines.[61] Patients with asthma COPD overlap syndrome (ACOS) were eligible based on the findings of a previous study.[44]
- A history of at least two exacerbations requiring treatment with antibiotics and/or oral corticosteroid use in the previous year, based on patient report.
- Clinically stable with no COPD exacerbation for at least 4 weeks.
- Able to swallow study medication.
- Able and willing to give informed consent to participate.
- Able and willing to participate in the study procedures, and complete study questionnaires.
- Able and willing to undergo spirometric assessment, and able to perform a FEV_1 manoeuvre as a minimum.

Potential participants with COPD who did not fulfil the lung function criterion of FEV_1/FVC < 0.7 at the recruitment/baseline visit were asked to complete a slow vital capacity (SVC) manoeuvre and FEV_1/SVC < 0.7 was accepted as evidence of airflow obstruction.

During the COVID-19 pandemic when infection prevention and control (IPC) considerations made it unsafe to perform spirometry, potential participants did not need to fulfil the criterion of willing and able to undergo spirometric assessment, and historical evidence in the medical notes of FEV_1/FVC < 0.7 and FEV_1 < 80% predicted was accepted instead of performing spirometry at baseline to confirm FEV_1 < 80% predicted, FEV_1/FVC < 0.7.

During the COVID-19 pandemic, people with COPD were advised to shield from March 2020, and there were anecdotal reports and subsequent evidence that the incidence of exacerbations experienced by people with COPD declined by as much as 50%.[62,63] Given the evidence that the frequent exacerbator phenotype is stable for at least 3 years,[29] the inclusion criterion of 'a history of at least two exacerbations in the previous year' was modified post March 2020 to 'a history of at least two exacerbations within 12 months of each other requiring treatment with antibiotics and/or oral corticosteroid since March 2019'.

Eligibility for inclusion was confirmed by a medically qualified person.

Exclusion criteria

The exclusion criteria for BICS were typical of studies of people with COPD but also included criteria specific for bisoprolol. Potential participants were excluded if they fulfilled any of the following criteria.

- A current sole respiratory diagnosis of asthma.
- Any diagnosis of asthma before the age of 40 years.
- A predominant respiratory disease other than COPD.
- Any significant disease/disorder which, in the investigator's opinion, either puts the patient at risk because of study participation or may influence the results of the study or the patient's ability to participate in the study.
- Previous allocation of a randomisation code in the study or current participation in the active intervention phase of another interventional study.
- Already taking beta-blocker.
- Known or suspected hypersensitivity to beta-blocker.
- For women, current pregnancy or breastfeeding, or planned pregnancy during the study.
- Unable to perform spirometry (FEV_1 manoeuvre).
- Current resting (5 minutes sitting) heart rate < 60 b.p.m.
- Current resting (5 minutes sitting) systolic blood pressure < 100 mmHg.
- Second, third-degree heart block (unless pacemaker in situ).
- Conditions for which beta-blocker use is a guideline recommendation, that is heart failure, or within the last year: myocardial infarction, acute coronary syndrome.
- Current tachyarrhythmia or bradyarrhythmia (including sick sinus syndrome, sinoatrial block) requiring treatment.

- Current treatment with interacting drugs:
  - heart rate-limiting drug such as calcium channel blockers (diltiazem, verapamil, ivabradine)
  - class-I antiarrhythmic drugs (e.g. quinidine, disopyramide; lidocaine, phenytoin; flecainide, propafenone)
  - centrally acting antihypertensive drugs (e.g. clonidine methyldopa, moxonidine, rilmenidine).[64]

- Severe peripheral arterial occlusive disease, severe forms of Raynaud syndrome.
- Conditions that are known to be triggered by beta-blockers or beta-blocker withdrawal including myasthenia gravis, periodic hypokalaemic paralysis, pheochromocytoma, thyrotoxicosis and psoriasis/history of psoriasis.
- People lacking capacity.

Long-term oxygen therapy was not an exclusion criterion and being unable to perform spirometry was not applicable during the COVID-19 pandemic when spirometry was not performed as part of the study because of IPC considerations.

Identification

Potential participants were recruited from both primary and secondary care sites across the UK and to ensure generalisability of the study, the intention was that the majority of participants (> 50%) would be recruited from primary care. Recruitment strategies differed between centres depending on local geographic and NHS organisational factors.

Primary care and other community-based services

In England recruitment from General Practices was conducted in conjunction with the NIHR Clinical Research Network (CRN) at both the national and local level. In Scotland, the Scottish Primary Care Research Network undertook the role undertaken by the English CRN by identifying potential participants in primary care.

For General Practices, the local CRN/collaborating recruitment site/trial office liaised directly with the practices who performed database searches (based on search criteria including one exacerbation treated with oral corticosteroids in previous year, interacting medications, comorbidities) to identify potential participants. Potentially suitable participants were sent an invitation letter and a short, one page, participant information leaflet (PIL).

For General Practices acting as Participant Identification Centres (PICs), the short PIL provided a range of methods (telephone, text, e-mail, reply-paid envelope) for interested potential participants to contact the local primary or secondary care trial centre for more information (including a more comprehensive 'long' PIL) and, if still interested, to arrange a recruitment assessment. For General Practices acting as independent study sites, the short PIL directed interested potential participants to contact the practice-based trial team for more information and to arrange a recruitment assessment.

In some areas, COPD Community Matrons, Pulmonary Rehabilitation classes and other Integrated/Intermediate Care services for patients with COPD distributed invitation letters and short PILs to potential participants. These materials directed interested potential participants to local trial centres in primary and secondary care.

Secondary care

Potential participants were also identified from patients who were attending (or who had previously attended) respiratory outpatient appointments or had been inpatients at the hospitals of the individual recruiting centres. Potential participants could be approached by a member of the care team during a clinical episode to explain the study and to provide them with a short PIL that provided a range of methods for interested potential participants to contact the local trial team (e.g. telephone, text, e-mail, reply-paid envelope) for more information and, if interested, to arrange a recruitment assessment. Alternatively, they could be invited by post.

In secondary care sites with a Volunteer Database/Registry, potential participants, meeting the essential study eligibility criteria, were sent a letter of invitation and short PIL. Potentially interested participants were directed to make contact with the local secondary care trial team for further information and to arrange a recruitment assessment.

All invitation material, consent forms, trial case report forms and participant-completed questionnaires are included in *Report Supplementary Material 1*.

Recruitment/baseline assessment

Prior to COVID-19, in both primary and secondary care, recruitment assessment was a face-to-face visit, whereas during the COVID-19 pandemic period when recruitment restarted, the recruitment assessment could be face to face or conducted by telephone or video call, depending on the potential participant's preference.

At the recruitment/baseline assessment, the participant's eligibility was confirmed by a medically qualified doctor and fully informed consent was recorded in writing. Baseline data were also collected.

Pre-COVID-19 pandemic

Recruitment/baseline assessments undertaken before March 2020 and the COVID-19 pandemic were conducted face to face, either in primary or secondary healthcare facilities or in the participant's home. Written informed consent was obtained from the participants by an appropriately trained individual listed on an appropriate delegation log.

During COVID-19 pandemic

During the COVID-19 pandemic, as part of the national COVID-19 response, people with COPD were deemed vulnerable and advised to shield at home, in addition physical access to primary and secondary healthcare facilities was greatly reduced. When recruitment into the BICS re-started, face-to-face recruitment assessments could still be conducted in primary or secondary healthcare facilities or the participant's home, with appropriate COVID-19 measures in place [personal protective equipment (PPE), social distancing], or by telephone or video call.

Where recruitment was done without a face-to-face appointment, potential participants who expressed an interest in taking part in the study after receiving the short PIL were initially contacted by telephone or video call (first consultation), during which all aspects of the study were discussed. If still interested, a second telephone or video consultation was arranged and a comprehensive 'long' PIL, consent form and reply-paid envelope were posted out to them. During the second telephone or video consultation, participants were asked to complete, sign and date the consent form and return it to the trial team in the provided reply-paid envelope. Once received by the trial team, the person who carried out the informed consent discussion countersigned the consent form. Once the consent form had been received, a sphygmomanometer (along with pregnancy test for women of childbearing potential) was posted to the participant and a third telephone or video consultation arranged, during which the participant was told/shown how to use the sphygmomanometer, and baseline data including heart rate and blood pressure were recorded.

Randomisation/treatment allocation

After providing written informed consent, participants were randomised by a member of the research team at the recruitment site. Participant were allocated to a treatment group using a computerised web-based randomisation service embedded within the trial website (https://w3.abdn.ac.uk/hsru/BICS/Public/Public/index.cshtml). The randomisation service was created and administered by the Centre for Healthcare Randomised Trials (CHaRT), University of Aberdeen. It was only possible to randomise a participant if the relevant eligibility criteria had been met and confirmed in the database. The randomisation was stratified by trial centre (or area for primary care sites), and recruitment setting (primary or secondary care) and participants were randomised with equal probability (1 : 1) to the intervention and control groups.

The randomisation process assigned a study number (participant ID), allocated a treatment, and assigned a drug pack. The user was notified, on screen, of the study number and drug pack that were then used to write a study drug prescription (signed by a delegated medical professional) in order for the study medication to be dispensed and delivered to the participant. Trial participants, care providers, outcome assessors, trials managers and data analysts remained blinded to allocation status until database lockdown. Unblinding of allocation status was permitted to enable treatment of severe adverse events, overdose, or to enable suspected unexpected serious adverse event (SUSAR) reporting. For a period of time during the study, the Data Monitoring Committee (DMC) were provided with unblinded SAEs in real time. The protocol also had provision for participants or their GPs to ask for the treatment allocation code at the end of the treatment period to help plan future treatment – in such cases, the trial staff remained blind to the

allocation. Site staff had access to the unblinding facility. For out of office hours unblinding, the clinicians providing out of hours cover were also allowed access to the unblinding facility. All the data captured or assigned were saved to a secure database.

The random allocation sequence was generated using permuted blocks to provide randomly generated blocks of entries of varying sizes permuted for each combination of region and recruitment setting (primary or secondary care). Each entry was assigned a treatment according to a randomly generated sequence utilising block sizes of 2 or 4. Each treatment option was assigned an equal number of times within each block, ensuring that the total entries assigned to each treatment remained balanced. The sequence of blocks was also random, so it was not possible to determine the next treatment to be allocated based on previous allocations made during the randomisation process. The random permuted blocks defining treatment allocation were created by the CHaRT programming team during system development. The system built to utilise these permuted blocks was tested by a run of simulated randomisations, which allowed the outcomes to be cross-checked and validated. Before the randomisation system went 'live', enough blocks were created to ensure entries existed for the maximum expected number of participants across the maximum expected number of trial centres/areas.

Intervention

The intervention was either the cardioselective beta-blocker bisoprolol (1.25 mg tablets) or identical placebo taken for 52 weeks. The bisoprolol and placebo tablets were white, film-coated, round, biconvex tablets with a diameter of 9 mm and packaged in bottles of 168 tablets labelled with the same batch number and expiry date. Bisoprolol and placebo were manufactured by Tiofarma BV (Oud-Beijerland, Netherlands) and supplied by Mawdsley-Brooks & Co. (Doncaster, UK).

Bisoprolol is licensed for the treatment of stable chronic heart failure with reduced systolic left ventricular function. The expected side effects of bisoprolol are listed in *Table 1*.[64]

Dose titration

To ensure participant safety and to minimise the risk of side effects, the study drug was started at a low dose (1.25 mg/1 tablet once a day) and slowly up titrated (i.e. weekly increments of 1.25 mg → 2.5 mg → 3.75 mg → 5 mg) resulting in final doses of bisoprolol of 1.25 mg once daily (1 tab), 2.50 mg once daily (2 tabs), 3.75 mg once daily (3 tabs) or 5 mg once daily (4 tabs) depending on tolerance to bisoprolol up-dosing. The equivalent final placebo doses were 1, 2, 3 or 4 tablets a day. Participants completed the remainder of the 52-week treatment period on the final titrated dose unless modified by the local research for clinical reasons and/or participant request.

The dose-titration schedule was a conservative interpretation of the 'start low, go slow' advice provided in the summary of product characteristics (SmPC) for bisoprolol and Heart Failure Guidelines designed for use by appropriately trained nurses in primary care settings and is summarised in *Figure 3*.[41,64–66] The first study bottle containing 168 tablets enabled dose titration to be undertaken during the first 7 weeks of the treatment period. This was designed to reflect everyday clinical practice and the need to give the participant and research team flexibility to respond to clinical (e.g. side effects, exacerbations) and practical issues (e.g. participant availability, holidays). The minimum time between each dose-titration visit/assessment was 7 days, and a maximum of four dose-titration visits/assessments were permitted, the actual number being primarily determined by tolerance to the study medication.

Prior to commencing treatment, participants were informed not to expect immediate improvement because any benefit was likely to be reflected in reduced exacerbations and that any symptomatic deterioration (fatigue, tiredness) occurring after starting/increasing study medication would be easily managed by adjustment of study medication dose (usually to previous tolerated dose). The research teams were advised that it was not possible to reliably establish in an individual the treatment allocation from heart rate, blood pressure, because in previous studies of bisoprolol in heart failure, similar proportions of patients allocated to placebo and bisoprolol were unable to tolerate treatment.[67]

TABLE 1 Expected side effects of bisoprolol

System	Side effect	Incidence
Cardiac	Bradycardia	Very common (≥ 1/10)
	Worsening of heart failure	Common (≥ 1/100, < 1/10)
	Atrioventricular conduction disturbances	Uncommon (≥ 1/1000, < 1/100)
Nervous system	Dizziness, headache	Common (≥ 1/100, < 1/10)
	Syncope	Rare (≥ 1/10,000, < 1/1000)
Gastrointestinal	Nausea, vomiting, diarrhoea, constipation	Common (≥ 1/100, < 1/10)
Vascular	Coldness/numbness in the extremities	Common (≥ 1/100, < 1/10)
	Hypotension	Common (≥ 1/100, < 1/10)
General	Asthenia, fatigue	Common (≥ 1/100, < 1/10)
Respiratory	Worsening airflow obstruction	Uncommon (≥ 1/1000, < 1/100)
	Allergic rhinitis	Rare (≥ 1/10,000, < 1/1000)
Musculoskeletal	Muscle weakness, muscle cramps	Uncommon (≥ 1/1000, < 1/100)
Psychiatric	Sleep disorders, depression	Uncommon (≥ 1/1000, < 1/100)
	Nightmares, hallucinations	Rare (≥ 1/10,000, < 1/1000)
Eyes	Reduced tear flow	Rare (≥ 1/10,000, < 1/1000)
	Conjunctivitis	Very rare (< 1/10,000)
Ears	Hearing disorders	Rare (≥ 1/10,000, < 1/1000)
Skin	Itching, flush, rash	Rare (≥ 1/10,000, < 1/1000)
	Psoriasis-like rash	Very rare (< 1/10,000)
	Alopecia	Very rare (< 1/10,000)
Hepatobiliary	Hepatitis	Rare (≥ 1/10,000, < 1/1000)
Reproductive	Potency disorders	Rare (≥ 1/10,000, < 1/1000)

Prior to the COVID-19 pandemic when the dose-titration assessments were face to face, decisions to increase, reduce or to fix on a dose during the titration period were determined by participant reports of intolerable side effects, measured heart rate, measured systolic blood pressure and measured FEV_1. Participants who were in the titration phase when the pandemic was first declared did not complete their full titration phase but were fixed on their last (or current) tolerated dose. When recruitment restarted, dose-titration assessments were conducted over the telephone or by video call, and decisions to increase, reduce or to fix on a dose during the titration period were determined by participant reports of intolerable side effects, measured heart rate, measured systolic blood pressure and participant reports of any worsening in breathlessness since any dose increase. Heart rate and blood pressure were measured by the participant using a digital sphygmomanometer provided by the study.

A computerised advisory titration algorithm was incorporated into the study website (detailed in *Report Supplementary Material 3*). This algorithm also included participant's self-reported adherence with study medication and whether (s)he wished to increase, decrease or fix a dose. Site staff were advised that they could follow the computer titration advice or make an alternative clinical decision.

Following completion of the 52-week treatment period, to avoid any risk of rebound tachycardia, hypertension or angina, participants were weaned off study medication over the ensuing 3 weeks (3-2-1 tablet once daily), with cessation of study medication being confirmed by a telephone contact. During the treatment period, participants were

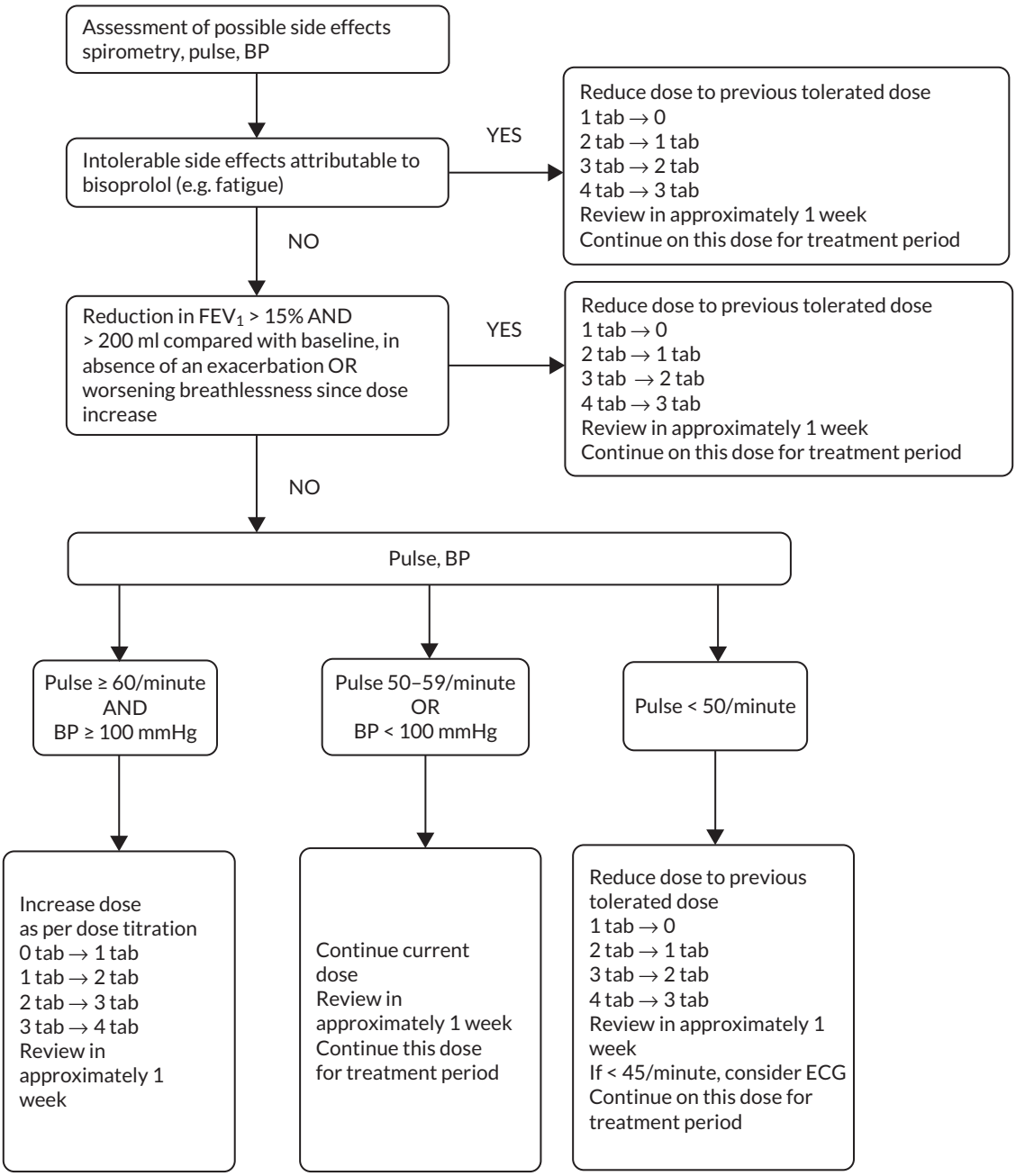

FIGURE 3 Schematic representation of dose titration. BP, blood pressure; ECG, electrocardiogram.

advised not to abruptly stop study medication but to make contact with their study team who weaned them off by one tablet a day per week to zero. If clinically indicated, clinicians were allowed to abruptly stop study medication, for example, development of tachyarrhythmia, diagnosis of heart failure.

Supply of study medication

Study medication was packaged into bottles of 168 tablets and stored at Mawdsley-Brooks & Co. and shipped to the central Clinical Trials Pharmacy in NHS Grampian. Drug packs were sent by the Clinical Trials Pharmacy to the participants' homes using a 'signed for delivery' courier service. The signature obtained upon delivery was checked by the central trial office. Participants provided written consent for the use of personal details for the purposes of

couriering the study medication. The first drug pack of 168 tablets was couriered to a participant's home address soon after enrolment and randomisation. After the final dose of study medication was established during the dose-titration phase and entered into the study website, this triggered a second prescription, and the dispensing and couriering of further supplies of study medication from the central Clinical Trials Pharmacy to the participant's home. The second supply of study medication was sufficient to cover 24 weeks of the treatment period and equated to one bottle (168 tablets) for each 1.25 mg bisoprolol or placebo equivalent, for example 2.5 mg = 2 bottles, 5 mg = 4 bottles. The second supply of study medication occurred 20 weeks into the treatment period. A third prescription was triggered; the medication dispensed and was couriered to the participant's home address.

Data collection

Baseline, outcome and safety data were collected by assessments conducted at recruitment/baseline (week 0), week 26 and week 52 and entered into electronic case report forms embedded in the study website (https://w3.abdn.ac.uk/hsru/BICS/Public/Public/index.cshtml) created and administered by the CHaRT, University of Aberdeen. Recruitment sites were given the option of entering data directly into the electronic database or to enter the data onto paper forms and then into the electronic database. Up to four dose-titration assessments were conducted in the first 7 weeks of the treatment period, during which safety and outcome data were also collected. Participants had any travel expenses reimbursed; they received no other payments. The schedule for data collection within the study is outlined in *Table 2*.

As described above, prior to the COVID-19 pandemic, these assessments were conducted face to face usually in a health facility or less often within participants' homes. During the COVID-19 pandemic, when people with COPD were advised to shield, assessments were usually conducted by telephone or video call, although sites were still given the option to conduct face-to-face assessments with appropriate precautions in place (PPE, social distancing, hand hygiene, etc.) for recruitment or if there were clinical concerns.

Demographic, clinical data

Demographic, contact and clinical history data were captured at the recruitment assessment.

Drug history

Regular use of prescription drugs was recorded at recruitment and the 26- and 52-week assessments. Most participants brought their repeat prescription list with them to assessments.

Smoking history

Smoking history was recorded at recruitment.

Height

Height was measured using clinic stadiometer at recruitment if conducted face to face. For telephone/video-call assessments, self-reported height was recorded.

Weight

Weight was measured using clinic scales at recruitment if conducted face to face. For telephone/video-call assessments, self-reported weight was recorded.

Heart rate

Resting heart rate was recorded at recruitment, the dose-titration assessments at week 1, 2, 3, 4 and the 26- and 52-week assessments. For telephone/video-call assessments, these were measured by the participant using a digital sphygmomanometer provided by the study.

Blood pressure

Blood pressure was measured using a sphygmomanometer and recorded at recruitment, the dose-titration assessments at week 1, 2, 3, 4 and the 26- and 52-week assessments. For telephone/video-call assessments, these were measured by the participant using a digital sphygmomanometer provided by the study.

TABLE 2 Schedule of study assessments

Assessment	Recruitment	1 week	2 weeks	3 weeks	4 weeks	Month 6	Month 12	Post study GP records	Post weaning/ final dose
Assessment of eligibility criteria	●								
For women of childbearing potential – pregnancy test	●				●	●	●		
Written informed consent	●								
Confirmation that participant is content to continue in the trial		●	●	●	●	●			
Demographic data, contact details	●								
Clinical history	●								
Drug history	●					●	●		
Smoking status	●								
Height[a]	●								
Weight[a]	●								
Pulse/heart rate[b]	●	●	●	●	●	●	●		
Blood pressure[b]	●	●	●	●	●	●	●		
Total number COPD exacerbations requiring oral corticosteroids/antibiotics						●	●	●	
Hospital admissions						●	●	●	
Health-related quality of life	●					●	●		
Disease-related health status (CAT, BDI/TDI dyspnoea)	●					●	●		
HARQ (some centres only)	●					●	●		
Post-bronchodilator lung function[c]	●	●	●	●	●	●	●		
Adverse events/drug reactions		●	●	●	●	●	●		
Major adverse cardiac events						●	●		
Healthcare utilisation	●					●	●		
Patient compliance		●	●	●	●	●	●		
Telephone call to confirm cessation of study drug									●

a Self-reported height and weight recorded during telephone/video-call assessments.
b For telephone/video-call assessments, measured by participant using a supplied digital sphygmomanometer.
c During the COVID-19 pandemic, lung function (an aerosol-generating procedure) was not assessed.

Number of chronic obstructive pulmonary disease exacerbations

The primary outcome measure of the total number COPD exacerbations requiring antibiotics/oral corticosteroids while on study medication was ascertained at the 26- and 52-week assessments; however, any exacerbations occurring during the dose-titration phase were also recorded during dose-titration assessments at 1, 2, 3, 4 weeks. Participants were encouraged to record any exacerbations on a provided 'reminder card' and to have this available during their follow-up assessments. For those participants where follow-up at 26 and/or 52 weeks could not be completed, GPs

were contacted and asked to provide information on the number of exacerbations experienced by the participant in the treatment period, and whether or not these resulted in hospital admission.

The ATS/ERS guideline definition of COPD exacerbation was used: a worsening of patient's dyspnoea, cough and/or sputum beyond day-to-day variability sufficient to warrant a change in management.[68] The minimum management change was treatment with antibiotics and/or oral corticosteroids. A minimum of 2 weeks between consecutive hospitalisations/start of new therapy was necessary to consider events as separate. A modified ATS/ERS operational classification of exacerbation severity was used for each exacerbation: Level I, increased use of short-acting beta2 agonist (SABA); Level II, use of oral corticosteroids or antibiotics; Level III, care by services to prevent hospitalisation; Level IV, admitted to hospital.[68] Given our definition of exacerbation, Level II and above exacerbations contributed to the primary outcome.

Hospital admissions

The number of unscheduled hospital admissions while on study medication was ascertained at the 26- and 52-week assessments. Emergency admissions because of COPD were also identified. Between assessments, participants were encouraged to record any hospital admissions on the reminder card, and to have this available during their follow-up assessments. Attempts were also made to check GP records for all participants who did not complete the 52-week assessment or did not complete a postal questionnaire.

Major adverse cardiovascular events

Major adverse cardiovascular event as defined by cardiovascular death, hospitalisation for myocardial infarction, heart failure, or stroke, percutaneous coronary intervention or coronary artery bypass grafting[69] was ascertained at the 26- and 52-week assessments and review of the SAE data. As for exacerbations of COPD and hospital admissions, GP records were checked for all participants who did not complete the 52-week assessment or did not complete a postal questionnaire.

Health-related quality of life

Health-related quality of life data were captured at recruitment and at the 26- and 52-week assessments using EQ-5D-5L Index.[70] EQ-5D-5L was developed as a utility questionnaire and addresses mobility, self-care, usual activities, pain/discomfort and anxiety/depression, and it has been used widely in studies of COPD and can be used to compute QALYs through published UK tariffs.

Disease-related health status

At recruitment and at the 26- and 52-week assessments, the CAT questionnaire was used to quantify impact of COPD on health and daily well-being.[71–73] The CAT comprises eight questions and scores range from 0 to 40; it correlates well with scores from the longer St George Respiratory Questionnaire and has been shown to be reliable and responsive.

To assess any impact of study medication on the major COPD symptom of breathlessness, research nurses asked open-ended questions about the symptom of breathlessness in order to complete the BDI questionnaire at recruitment and the TDI questionnaire at the 26- and 52-week assessments.[74] BDI and TDI were developed in order to obtain a comprehensive understanding of patients' severity of breathlessness and are based on three components: functional impairment, magnitude of task and magnitude of effort.[74] BDI is a discriminative instrument used to quantify the severity of dyspnoea at an initial or baseline state, whereas TDI is an evaluative instrument used to quantify the changes in dyspnoea from the initial or baseline state.[75]

In selected centres, the HARQ was used to assess symptoms not elucidated by the CAT or dyspnoea index. This is a validated self-administered questionnaire that is responsive to treatment effects.[76]

Post bronchodilator lung function

Prior to the COVID-19 pandemic, lung function was measured by spirometry performed to ATS/ERS standards at recruitment, dose-titration visits, and 26- and 52-week visits.[77] Spirometry is a routine part of the clinical assessment of people with COPD. Post bronchodilator [long-acting beta2 agonist (LABA) within 8 hours, SABA within 2 hours] FEV_1 and FVC was measured using lung function equipment usually used in clinical practice. If necessary, lung function was

measured 15 minutes after administration of the participant's own SABA. The European Coal and Steel Community predictive equations were used to compute predicted values for FEV_1 and FVC.[78]

During the COVID-19 pandemic, lung function was not performed because spirometry was designated as an aerosol-generating procedure and could not be justified for the study. At recruitment, spirometry was replaced by historical evidence in the medical records of FEV_1/FVC < 0.7 and FEV_1 < 80% predicted, and at the dose-titration assessment, spirometry was replaced with participant report of any change in the severity of any breathlessness since the study medication was either started or the dose of study medication was increased.

Healthcare utilisation

Healthcare utilisation during the previous 6 months was ascertained at recruitment and the 26- and 52-week assessments using a modified version of the Client Service Receipt Inventory (CSRI).[79] The CSRI is a research questionnaire for retrospectively collecting cost-related information about participant's use of health and social care services.

Adverse reactions and serious adverse events

This trial complied with the UK National Health Service Health Research Authority guidelines for reporting adverse events.[80] ARs and SAEs occurring during the 52-week treatment period were ascertained at the 1-, 2-, 3-, 4-week dose-titration assessments, and the 26- and 52-week assessments. Participants were informed of recognised ARs during the process of informed consent (verbally and in the PIL) and encouraged to contact the local study centre if they experienced these. ARs and SAEs were recorded from the time a participant consented until the end of the weaning period after the 52-week follow-up. Participants who withdrew from taking the study medication had any ARs/SAEs recorded until 28 days after ceasing study medication. Any deaths occurring during the 52-week follow-up period were recorded as a SAE.

Hospitalisations for treatment planned prior to randomisation and hospitalisations for elective treatment of pre-existing conditions were not considered or recorded or reported as a SAE. Complications occurring during such hospitalisation were also not considered, recorded or reported as a SAE – unless there was a possibility that the complication arose because of the study medication (i.e. a possible AR). Exacerbations of COPD or hospital admissions as a consequence of exacerbations of COPD were not considered, recorded or reported as AEs or SAEs because these were primary/secondary outcomes. Admissions to hospital because of pneumonia or COVID-19 were captured as SAEs.

Serious adverse events were assessed as to whether the SAE was likely to be related to the treatment using the following definitions:

- Unrelated: where an event is not considered to be related to the study drug.
- Possibly: although a relationship to the study drug cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible.
- Probably: the temporal relationship and absence of a more likely explanation suggest that the event could be related to the study drug.
- Definitely: the known effects of the study drug or its therapeutic class, or based on challenge testing, suggest that study drug is the most likely cause.

The reference safety information used to assess whether or not the event was expected was that listed in the SmPC for bisoprolol[64] and outlined in *Table 1*. The reference safety information was also used to develop the Case Report Form (CRF) to capture ARs.

Serious adverse events and ARs were Medical Dictionary for Regulatory Activities (MedDRA) coded to System Organ Class (SOC) level.[81]

Compliance

Compliance/adherence with study medication was assessed at the 1-, 2-, 3- and 4-week dose-titration assessments and the 26- and 52-week assessments. Prior to the COVID-19 pandemic, participants were asked to estimate compliance/

adherence at the dose-titration assessments, and for the 26- and 52-week assessment, participants were asked to return empty drug bottles and compliance was calculated by pill counting.[82] During the COVID-19 pandemic, pill counting was not possible and participants were asked to estimate compliance/adherence. Participants were asked how frequently they had been taking their study tablets since the last visit. The responses were classified as 'Every day', 'Not every day but more than 70% of the time', 'Less than 70% of the time' and 'Not taken any since last visit', and participants were to report how many tablets they had taken on the days that they had taken them.

Participant withdrawal

Reasons for participants withdrawing from treatment were:

- Withdrawal of consent for treatment.
- Unacceptable adverse effects.
- Intercurrent illness preventing further treatment.
- Development of serious disease preventing further treatment or any change in the participant's condition that justified the discontinuation of the study medication, the opinion of a clinician; for example, diagnosis of lung cancer.
- Development or diagnosis of a condition needing treatment with beta-blockers; for example, acute coronary syndrome, heart failure, tachyarrhythmias.

Participants who withdrew from the treatment and agreed to remain in the study for follow-up were followed up at 26 and 52 weeks, either in a face-to-face assessment or by telephone/video call. Participants declining formal follow-ups were asked if they were agreeable to 'remote' follow-up using hospital/GP medical records.

Sample size

The original intent of the study was to recruit and randomise 1574 participants, with at least 50% being recruited in primary care.

The sample size calculation was based on the multicentre ECLIPSE study that reported the frequency of COPD exacerbation in 2138 patients.[29] For patients identical to our target population (≥ 2 self-reported COPD exacerbations in a year requiring antibiotics and/or oral corticosteroids), the mean (SD) number of COPD exacerbations within the subsequent 1 year was 2.22 (1.86) (Dr Nick Locantore, ECLIPSE statistician, personal communication). Subsequent to the current study commencing recruitment, we reported the findings of our study of low-dose theophylline in people with COPD [theophylline with inhaled corticosteroids (TWICS)] with ≥ 2 self-reported COPD exacerbations in a year requiring antibiotics and/or oral corticosteroids. In this study, the mean (SD) number of COPD exacerbations within the subsequent 1 year was 2.24 (1.99).[59] The Cardiac Insufficiency Bisoprolol Study II reported that about 15% of participants stopped taking study medication in a trial of bisoprolol versus placebo.[67]

Based on a mean (SD) number of 2.22 (1.86) COPD exacerbations in the placebo arm, 787 participants were needed in each treatment group (i.e. 1574 in total) to detect a clinically important reduction in COPD exacerbations of 15% (i.e. from an average of 2.22 to 1.89), with 90% power at the two-sided 5% significance level and allowing for 15% withdrawal from the study. As there is no validated or generally accepted minimal clinically important difference for COPD exacerbation frequency,[83,84] the clinically important 15% reduction in COPD exacerbations was decided upon for our trial of low-dose theophylline after consultation with primary and secondary care colleagues who considered a 15% reduction to be small but clinically important.[59]

As described later, this trial was affected by the COVID-19 pandemic and closed to recruitment in May 2022 after 519 participants had been enrolled when the funder indicated they could not fund the extension to the recruitment period that would have been required to meet the recruitment target of 1574. A post hoc analysis of study statistical power confirmed that the trial was underpowered having about 46% power to detect the pre-specified clinically important 15% reduction in exacerbations with $\alpha = 0.05$, consequently the study findings need to be interpreted with caution.

Statistical analysis

All analyses were pre-specified in a statistical analysis plan that was agreed by the Trial Steering Committee (TSC) and approved by the independent DMC prior to any analyses being undertaken. The statistical analysis plan is included in *Report Supplementary Material 2*. Unless pre-specified, a 5% two-sided significance level was used to denote statistical significance throughout, and estimates are presented alongside their 95% CIs. No adjustments were made for multiple testing. All analyses were according to the intention-to-treat (ITT) principle with a per-protocol analysis performed as a sensitivity analysis. The per-protocol analysis excluded participants who were not compliant, with compliance being defined as taking 70% or more of their expected doses of study medication. The ≥ 70% definition of compliance was decided upon for our trial of low-dose theophylline in COPD after consultation with primary and secondary care colleagues, who considered that in the absence of an accepted definition, a 70% figure for compliance was a 'clinically sensible'.[60] Analyses were performed using R Statistical Software version 4.2.1 (R core team, Vienna, Austria).[85]

Categorical variables are described with number and percentage in each category. Continuous variables are described with mean and SD if normally distributed, and median and interquartile range (IQR) if skewed. The amount of missing data is reported for each variable.

Primary outcome

The primary outcome (number of COPD exacerbations requiring antibiotics and/or oral corticosteroids in the 12-month treatment period following randomisation) was compared between randomised groups using a generalised linear mixed model with the negative binomial distribution of the outcome and log-link function, along with an appropriate over-dispersion parameter and length of time in study as an offset.[86] The estimated treatment effect is presented as unadjusted rate ratio followed by adjusted rate ratio for a set of pre-specified baseline variables. The adjustment variables were centre (as a random effect), recruitment setting (primary or secondary care), age (in years) centred on the mean, gender (male/female), smoking status (pack years), FEV_1% predicted, number of COPD exacerbations in the year prior to randomisation, baseline COPD treatment [inhaled corticosteroid (ICS) (no/yes), LABA (no/yes) long-acting muscarinic antagonist (LAMA) (no/yes), and treatment with long-term antibiotics (no/yes)]. Participants who did not provide a full 12 months of follow-up information were included to the point at which they were lost to follow-up with their time in the study utilised in the offset variable.

To account for the impact of the COVID-19 pandemic (i.e. during the lockdown period) on the exacerbation rate,[62,63] three different approaches were taken to analyse the data:

1. Approach 1: Analysis of the data using the standard modelling approach outlined above. This approach assumes the COVID-19 pandemic did not happen; that is COVID-19 lockdown was an additional intervention strategy to prevent exacerbations of participants.
2. Approach 2: All outcome data were set to missing during the lockdown period (non-informative censoring), and all events related to stopping treatment were ignored. The modelling approach mentioned above was applicable except the offset time included the logarithm of the follow-up time until the lockdown day. This was applicable if a participant was still in the trial during the lockdown period (i.e. the offset excluded the complete length of the trial if a participant's follow-up time entered into the lockdown period). The data during the lockdown period were modelled as missing data assuming the data were missing completely at random.
3. Approach 3: The entire study period was partitioned into three periods: pre-lockdown, lockdown and post-lockdown. For each participant, the time of exacerbation events was assigned the appropriate period. In addition to the list of effects mentioned earlier, the statistical model included the period as the main effect and the two-way interaction term of treatment and period. If the global two-way interaction term was not statistically significant ($p < 0.05$), the term was removed from the model, and the marginal treatment and period effects estimated. The cluster-level standard error was estimated using the robust method.

Secondary outcomes

The total number of COPD exacerbations requiring hospital admission and the total number of emergency admissions (all causes) were analysed in the same way as the primary outcome. Quality-of-life measures (CAT, EQ-5D-5L, HARQ) and lung function (FEV_1 and FVC) collected at baseline, 26- and 52-week follow-up were compared between randomised groups using a linear mixed-effects model, unadjusted and adjusted for the same pre-specified covariate set as described for the primary outcome. Fixed effects included assessment number, treatment and all the pre-specified as described above, with participant and participant–assessment interaction fitted as random effects. A treatment–assessment interaction was included to assess the differential treatment effect on rate of change in outcome. All participants within the ITT population were included in the analysis, and missing outcome data assumed to be missing at random. Breathlessness using the TDI collected at 26 and 52 weeks was analysed using a linear mixed-effects model (as described for the quality-of-life measures), with adjustment for BDI in addition to those listed for the primary outcome. All-cause mortality rate and COPD-related mortality and time to first exacerbation were compared between randomised groups using Kaplan–Meier survival curves and mixed Cox regression model, with adjustment for the pre-specified variables outlined above for the primary outcome. Estimates are presented as HR with 95% CIs. MACEs were compared between randomised groups using a chi-squared test.

Sensitivity analyses

The primary outcome was analysed between treatment groups defined as a binary variable (bisoprolol vs. placebo). To assess the impact of the actual dose of bisoprolol at the end of the dose-titration period (fixed dose), an exploratory analysis was undertaken for the primary outcome, taking into account the actual fixing dose to assess whether there is an element of dose–response relationship (whether certain doses have improved outcomes over others). To assess the impact of death, a sensitivity analysis was undertaken that excluded those participants who died during the treatment period. For participants who were lost to follow-up at some time during the 52-week treatment period, their data were included in the statistical models up to the point that they were lost to follow-up, using their time in the study as an offset.

Pre-specified subgroup analysis

The analysis for the primary outcome (using the standard modelling approach with no adjustment for COVID-19) was repeated for a number of subgroups. The subgroups were age (< 60, 60–69, ≥ 70 years), gender (male/female), body mass index (BMI) (< 18.5, ≥ 18.5 to < 25, ≥ 25 kg/m^2), smoking status at recruitment (ex/current), baseline treatment for COPD [triple therapy (ICS, LAMA, LABA), double therapy (ICS/LAMA or ICS/LABA), single therapy (ICS only)], GOLD stage (I–II, III, IV), exacerbations in 12 months prior to recruitment (2, 3–4, 5+), oral corticosteroids at recruitment (yes/no). Subgroup analysis was undertaken by the addition of a treatment–covariate interaction term and using the appropriate contrast to obtain group-specific estimates. We report observed mean (SD) exacerbations in each subgroup by treatment group, the treatment effect (IRR and 99% CIs) along with the *p*-value for the interaction term.

Health economics

The methods for the health economic analysis are described in *Chapter 5*.

Public and patient involvement

The BICS built on the public and patient involvement (PPI) in our previous study of low-dose theophylline in COPD (TWICS), for example, advice about what would be reasonable for people with COPD to do, what people with COPD expect from a trial, the need to deliver study medications to participants homes and the use of a one-page short PIL.[60]

Two members of the public greatly contributed to this study:

Mr Alastair Laird was a person living with severe COPD who had been admitted to hospital on several occasions for treatment of COPD exacerbations. He was an applicant on the original proposal and was actively involved in the development of this study. He was a member of the TSC; he attended TSC meetings and contributed to participant-facing materials. Sadly, Mr Alister Laird passed away in mid-2020.

Mr David Bertin was the Voices Scotland Lead for Chest Heart & Stroke Scotland (CHSS), who recruited a panel of 15 people living with COPD from CHSS's involvement database. After training the panel of COPD volunteers, he supported them so that they were able to voice opinions and ideas. Mr Bertin was a member of the TSC, where he not only provided support for Mr Laird but also presented the opinions and ideas of the panel of COPD volunteers who had been circulated with meeting materials beforehand by Mr Bertin. Mr Bertin and his panel of COPD volunteers made major contributions to the content and design of participant-facing materials, especially the PIL in which he memorably told us not to make the PIL look like a 'legalistic pass the buck exercise'. Unfortunately, during the COVID-19 pandemic, Mr Bertin was furloughed by CHSS and subsequently made redundant.

The study has been supported by CHSS and the (then) British Lung Foundation (BLF), the original outline proposal incorporated comments made by members of the BLF with COPD, co-ordinated by Dr Noel Snell, their Research Director.

The BICS trial was publicised in 2019 by a press release that included supportive quotes from the BLF and CHSS, and this publicity resulted in members of the public with COPD volunteering to participate, with their permission and their details passed on to their local BICS sites.

We were in the process of recruiting additional members of the public after COVID-19, but the decision that the study was considered unviable by the funder made this further recruitment unnecessary.

Protocol amendments

The study opened to recruitment on protocol version 4. Version 1 of the protocol was submitted for approval to the REC and MHRA before the combined review process was implemented. Version 2 of the protocol accommodated the changes required by the REC and version 3 accommodated changes required by the MHRA. Version 4 of the protocol brought the revisions made as part of version 2 and version 3 into a single updated version and incorporated additional changes. After the study opened to recruitment, there were four amendments to the protocol. Protocol version 5 included the immediate contingency arrangements in response to the COVID-19 pandemic (moving titration and follow-up visits from face to face to telephone). Protocol versions 6 and 7 is including changes to the protocol to allow for a restart to recruitment. Protocol version 8 included the information about early termination. *Appendix 1* describes the protocol revisions.

Trial oversight

A TSC, with independent members and PPI representation oversaw the conduct and progress of the trial in accordance with agreed terms of reference. An independent DMC oversaw the safety of participants within the trial. The terms of reference for the DMC included the periodic review of overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis. The DMC was permitted to review safety data in an unblinded fashion.

The trial was co-ordinated by a Project Management Group, consisting of the grant holders (Chief Investigator and other grant holders as appropriate), the Trial Manager, Statistician, Health Economist and other senior members of the Trials Unit (CHaRT).

Breaches

Breaches of trial protocol or good clinical practice were recorded and reported to the sponsor. A summary of breaches is included in *Appendix 2*. There were seven breaches reported within the BICS; one of these occurred in the cardiac substudy. All were assessed as non-serious and closed by the sponsor with appropriate corrective and/or preventive actions completed. Participants who were the subject of a breach remained in the ITT population, the safety population and the per-protocol population (if compliance criteria were met).

Unblindings

Two participants were unblinded as an emergency – both were experiencing tachycardia and treating clinician required allocation to plan treatment. Two further participants were unblinded for clinical reasons – one who had a new diagnosis of atrial fibrillation, and one who may have required an allergy alert placed on their medical records. Sixteen SAEs were unblinded in real time for DMC review after publication of Beta-Blockers for the Prevention of Acute Exacerbations of COPD (BLOCK COPD) trial raised safety concerns.[87] Five additional participants who experienced a SAE were unblinded at request of the sponsor for the purposes of SAE reporting. For two participants who died during follow-up, the Coroner or Procurator Fiscal requested the treatment allocation. At the end of their study follow-up, 21 participants (or their GPs) requested treatment allocation to inform future treatment.

Chapter 3 Baseline characteristics

Recruitment

In total, 110 sites were opened to recruitment across the UK prior to the COVID-19 recruitment pause (*Table 3*). Of these, 35 were secondary care sites and 75 were primary care sites. After the recruitment pause, 20 of these sites (10 secondary care, 10 primary care) re-opened to recruitment. An additional seven sites opened for the first time after the recruitment pause – one secondary care site and six primary care sites. Seventy-six sites recruited participants – 31 secondary care sites and 45 secondary care sites.

In total, 519 participants were recruited and randomised in the study. Between 17 October 2018 and 16 March 2020 (when the study paused to recruitment), 429 (82.7%) participants were recruited. A further 90 (17.3%) participants were recruited between 1 August 2021 (when the study re-opened to recruitment after people with COPD had been advised that they no longer needed to shield) and 31 May 2022 (when the study was closed to recruitment). Follow-up was completed 18 April 2023.

Two hundred and eight participants were identified in secondary care and recruited in secondary care, 133 were identified in primary care (via PICs) and recruited in secondary care, and 178 were identified and recruited in primary care (*Table 3*).

The number of participants recruited varied between sites. Within secondary care, the mean number of participants per site was 11, and the total number ranged from 1 to 94. Within primary care, the mean number of participants per site was 4, and the total number ranged from 1 to 14. *Appendix 3* shows recruitment at each recruitment site.

Post-randomisation exclusions

There were four post-randomisation exclusions. All were identified as not meeting the eligibility criteria before study medication was dispensed. Two participants were excluded because their FEV_1 was higher than 85% predicted. One participant had previously been prescribed bisoprolol and was having a trial period of discontinuation of bisoprolol

TABLE 3 Recruitment

	Secondary care sites	Primary care sites	Total
Sites			
Opened prior to the recruitment pause	35	75	110
Re-opened after the recruitment pause	10	10	20
Opened for the first time after the recruitment pause	1	6	7
Total number of sites opened to recruitment	36	81	117
Total number of sites that recruited participant(s)	31	45	76
Participants			
Recruited prior to the recruitment pause	279	150	429
Recruited after the recruitment pause	62	28	90
Total recruitment	341[a]	178	519

a One hundred and thirty-three of these were identified in primary care and recruited in secondary care.

– at the end of the month's discontinuation, they decided to restart bisoprolol rather than taking part in BICS. One participant had only had one exacerbation in the previous 12 months; soon after randomisation, they exacerbated and the intention was to include them, but they did not recover sufficiently to start study medication before the pause to recruitment.

Baseline characteristics

The baseline characteristics for the 515 included participants (after exclusion of the four post-randomisation exclusions) are presented in *Table 4*. At baseline, the bisoprolol and placebo groups were well-balanced in terms of demographic and disease characteristics.

The mean (SD) age of participants was 67.7 (7.9) years (see *Table 4*) with just over half (53.2%) being male. About one-third (31.1%) were current smokers; the remainder were ex-smokers. The mean (SD) pack years smoked was 45.2 (25.2) pack years. Mean (SD) 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) (see *Table 5*). Measurement of lung function at baseline revealed that the mean (SD) FEV_1 was 50.1 (19.1) per cent predicted. Using the GOLD classification of airflow obstruction,[1] 16.3% were classified as very severe COPD, 34.6% as severe, 43.5% as moderate and 5.4% as mild. The participants with mild airflow obstruction (FEV_1 ≥ 80% predicted) came to light at the end of the study, and investigation revealed that they had been included because their physician had used historical lung function data demonstrating (FEV_1 < 80% predicted) as confirmation of the relevant inclusion criterion (FEV_1 < 80% predicted) instead of the spirometry conducted on the day of recruitment. The decision to analyse the data from these participants was based on the trial being pragmatic (these patients would have been commenced on bisoprolol based on the historical data if bisoprolol was shown to be beneficial); moreover, if these participants had been recruited during the COVID-19 pandemic, they would have been included based on historical evidence of FEV_1 < 80% predicted without baseline spirometry.

TABLE 4 Baseline sociodemographic characteristics of participants

	Bisoprolol (*N* = 259)	Placebo (*N* = 256)	Overall (*N* = 515)
Sex			
Male (*N*, *n*, %)	259, 134 (51.7)	256, 140 (54.7)	515, 274 (53.2)
Age (*N*, mean, SD)	259, 67.7 (8.0)	256, 67.7 (7.7)	515, 67.7 (7.9)
Smoking status			
Current smoker (*N*, *n*, %)	259, 78 (30.1)	256, 82 (32.0)	515, 160 (31.1)
Ex-smoker (*N*, *n*, %)	259, 181 (69.9)	256, 174 (68.0)	515, 355 (68.9)
Pack years (*N*, mean, SD)	259, 45.1 (24.4)	256, 45.2 (26.0)	515, 45.2 (25.2)
BMI, kg/m^2 (*N*, mean, SD)	258, 26.4 (5.7)	254, 27.2 (6.6)	512, 26.8 (6.2)
BMI group[a]			
Underweight (*N*, *n*, %)	258, 15 (5.8)	254, 19 (7.4)	512, 34 (6.6)
Normal (*N*, *n*, %)	258, 89 (34.4)	254, 90 (35.2)	512, 179 (34.8)
Overweight (*N*, *n*, %)	258, 97 (37.5)	254, 67 (26.2)	512, 164 (31.8)
Obese (*N*, *n*, %)	258, 57 (22.0)	254, 78 (30.5)	512, 135 (26.2)

a BMI group: underweight (BMI < 18.5); normal (18.5 ≤ BMI < 25); overweight (25 ≤ BMI < 30); obese (BMI ≥ 30).

TABLE 5 Baseline clinical characteristics (part 1)

	Bisoprolol (*N* = 259)	Placebo (*N* = 256)	Overall (*N* = 515)
Exacerbations in the last 12 months (*N*, mean, SD)	259, 3.5 (1.8)	256, 3.6 (2.1)	515, 3.5 (1.9)
Exacerbations requiring hospitalisation in the last 12 months (*N*, mean, SD)	259, 0.4 (0.8)	256, 0.5 (1.1)	515, 0.5 (1.0)
FEV_1% predicted (*N*, mean, SD)	258, 49.2 (19.0)	256, 51.1 (19.1)	515, 50.1 (19.1)
FEV_1% predicted category			
80+% (GOLD mild) (*N*, *n*, %)	258, 16 (6.2)	256, 12 (4.7)	514, 28 (5.4)
50–79.9% (GOLD moderate) (*N*, *n*, %)	258, 100 (38.6)	256, 124 (48.4)	514, 224 (43.5)
30–49.9% (GOLD severe) (*N*, *n*, %)	258, 99 (38.2)	256, 79 (30.9)	514, 178 (34.6)
0–29.9% (GOLD very severe) (*N*, *n*, %)	258, 43 (16.6)	256, 41 (16.0)	514, 84 (16.3)
FVC% predicted (*N*, mean, SD)	256, 92.5 (163.5)	253, 84.6 (22.3)	509, 88.6 (116.9)
FEV_1/FVC ratio (*N*, median, IQR)	256, 44.6 (22.7)	253, 46.2 (22.0)	509, 45.6 (22.5)
Resting heart rate (*N*, mean, SD)	259, 82.2 (11.8)	256, 80.3 (12.4)	515, 81.3 (12.1)
Systolic BP (*N*, mean, SD)	259, 137.0 (18.9)	256, 135.8 (17.7)	515, 136.4 (18.3)
Diastolic BP (*N*, mean, SD)	259, 79.9 (10.7)	79.6 (9.5)	79.8 (10.1)
Recruitment of participants			
Pre-COVID-19 pandemic (*N*, *n*, %)	259, 213 (82.2)	256, 212 (82.8)	515, 425 (82.5)
During COVID-19 pandemic (i.e. after the recruitment pause) (*N*, *n*, %)	259, 46 (17.8)	256, 44 (17.2)	515, 90 (17.5)

BP, blood pressure

The inhaled therapies used by those allocated to bisoprolol and placebo were balanced (see *Table 6*). The majority of participants (73.8%) were prescribed the 'triple therapy' combination of ICS, LABA and LAMA at baseline, and a further 17.9% of participants were prescribed 'dual therapies' (11.1% LABA LAMA, 6.8% ICS LABA). In total, 89.6% of participants were prescribed a LAMA, 4.9%% of participants were prescribed long-term oxygen therapy and 12.2% the long-term antibiotic (azithromycin).

Comorbidities, as reported by participants, were relatively common and on the whole balanced between those allocated to bisoprolol and those allocated to placebo (see *Table 7*). Almost one in eight (12.2%) had a concurrent diagnosis of asthma made after the age of 40 years, and 6.8% of participants reported a diagnosis of bronchiectasis. Nearly one-third of participants (29.5%) reported a diagnosis of hypertension, 4.3% reported a diagnosis of ischaemic heart disease, 5.8% reported a previous cerebrovascular event and 1.9% reported a diagnosis of peripheral vascular disease. Almost one-third (28.7%) reported anxiety or depression treated in the last 5 years. Diabetes mellitus was reported by 10.7%, and 13.8% had a diagnosis of osteoporosis.

The mean (SD) score on the CAT was 22.4 (8.1), indicating that overall COPD was having a high impact on the health and well-being of participants (see *Table 8*). 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). The BDI was used to quantify breathlessness, and it was possible to assign a value for all but 19 participants (7 bisoprolol, 12 placebo). The mean (SD) BDI score was 6.6 (2.7). CAT scores, EQ-5D-5L and BDI were balanced between the two treatment groups.

TABLE 6 Baseline clinical characteristics (part 2): current treatment for COPD

	Bisoprolol (*N* = 259)	Placebo (*N* = 256)	Overall (*N* = 515)
ICS only (*n*, %)	1 (0.4)	4 (1.6)	5 (1.0)
ICS LABA (*n*, %)	22 (8.5)	13 (5.1)	35 (6.8)
ICS LABA LAMA (*n*, %)	192 (74.1)	188 (73.4)	380 (73.8)
LABA (*n*, %)	1 (0.4)	1 (0.4)	2 (0.4)
LAMA (*n*, %)	9 (3.5)	14 (5.5)	24 (4.7)
LABA LAMA (*n*, %)	26 (10.0)	31 (12.1)	57 (11.1)
SABA only (*n*, %)	5 (1.9)	1 (0.4)	6 (1.2)
SAMA (*n*, %)	1 (0.4)	0	1 (0.2)
Long-term antibiotics (*n*, %)	30 (11.6)	33 (12.9)	63 (12.2)
Long-term oxygen therapy (*n*, %)	16 (6.2)	9 (3.5)	25 (4.9)

SAMA, short-acting muscarinic antagonist.

TABLE 7 Baseline clinical characteristics (part 3): comorbidities

	Bisoprolol (*N* = 259)	Placebo (*N* = 256)	Overall (*N* = 515)
Asthma diagnosis after 40 (*n*, %)	28 (10.8)	35 (13.7)	63 (12.2)
Bronchiectasis (*n*, %)	17 (6.6)	18 (7.0)	35 (6.8)
Ischaemic heart disease (*n*, %)	11 (4.2)	11 (4.3)	22 (4.3)
Hypertension (*n*, %)	73 (28.2)	79 (30.9)	152 (29.5)
Diabetes mellitus (*n*, %)	22 (8.5)	33 (12.9)	55 (10.7)
Osteoporosis (*n*, %)	34 (13.1)	37 (14.5)	71 (13.8)
Anxiety/depression treated in last 5 years (*n*, %)	71 (27.4)	77 (30.1)	148 (28.7)
Cerebrovascular event (*n*, %)	13 (5.0)	17 (6.6)	30 (5.8)
Hypocholesteraemia (*n*, %)	75 (29.0)	70 (27.3)	145 (28.2)
Peripheral vascular disease (*n*, %)	4 (1.5)	6 (2.3)	10 (1.9)

The final doses of bisoprolol and placebo established by dose titration are presented in *Table 9*. In total, 17.1% 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%). The daily doses of tablets were balanced between those allocated to bisoprolol and placebo for final fixed doses of two and three tablets/day (2.5 mg and 3.75 mg bisoprolol, respectively). More participants allocated to bisoprolol were fixed on a dose of one tablet/day (1.25 mg) compared to the placebo group, whereas 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%).

TABLE 8 Baseline participant-reported symptoms and quality of life

	Bisoprolol (*N* = 259)	Placebo (*N* = 256)	Overall (*N* = 515)
CAT (*N*, mean, SD)	259, 22.7 (8.1)	256, 22.0 (8.0)	515, 22.4 (8.1)
CAT group			
Low (score 0–9) (*N*, *n*, %)	259, 15 (5.8)	256, 13 (5.1)	515, 28 (5.4)
Medium (score 10–19) (*N*, *n*, %)	259, 77 (29.7)	256, 92 (35.9)	515, 169 (32.8)
High (score 20–29) (*N*, *n*, %)	259, 113 (43.6)	256, 103 (40.2)	515, 216 (41.9)
Very high (score 30–40) (*N*, *n*, %)	259, 54 (20.8)	256, 48 (18.8)	515, 102 (19.8)
EQ-5D-5L utility (*N*, mean, SD)	256, 0.59 (0.26)	252, 0.58 (0.25)	508, 0.59 (0.25)
EQ-5D-5L VAS (*N*, mean, SD)	257, 61.4 (21.3)	253, 60.9 (20.7)	510, 61.2 (21.0)
BDI (*N*, mean, SD)[a]	252, 6.6 (2.8)	244, 6.6 (2.7)	496, 6.6 (2.7)

VAS, visual analogue scale.
a Missing values include those for whom it was not possible to assign a BDI score.

TABLE 9 Final doses of bisoprolol and placebo fixed upon by dose titration, expressed as number of tablets per day

	Bisoprolol (*N* = 259)	Placebo (*N* = 256)	Overall (*N* = 515)
Fixed on 0 tablet/day (*n*, %)	46 (17.8)	42 (16.4)	88 (17.1)
Fixed on 1 tablet/day (bisoprolol 1.25 mg) (*n*, %)	62 (23.9)	28 (10.9)	90 (17.5)
Fixed on 2 tablets/day (bisoprolol 2.5 mg) (*n*, %)	41 (15.8)	43 (16.8)	84 (16.3)
Fixed on 3 tablets/day (bisoprolol 3.75 mg) (*n*, %)	37 (14.3)	32 (12.5)	69 (13.4)
Fixed on 4 tablets/day (bisoprolol 5 mg) (*n*, %)	71 (27.4)	110 (43.0)	181 (35.1)
Dose not fixed[a]	2 (0.8)	1 (0.4)	3 (0.6)

a Contact with one participant was lost soon after randomisation, and two participants died before a dose could be fixed.

Chapter 4 Clinical effectiveness

Clinical effectiveness of bisoprolol compared to placebo

This trial was affected by the COVID-19 pandemic and closed to recruitment in May 2022 after 519 participants had been enrolled when the funder indicated they could not fund the extension to the recruitment period that would have been required to meet the recruitment target of 1574. Consequently, the trial is significantly underpowered and the study findings need to be interpreted with caution.

In total, 519 participants were randomised to bisoprolol or placebo, with four post-randomisation exclusions resulting in 515 participants eligible to initiate study medication by entering dose titration and for whom baseline characteristics have been presented in *Chapter 3*. A consequence of the dose-titration process was that follow-up data were available for 514 (99.8%) participants, for bisoprolol, the duration of follow-up ranged from 14 to 365 days (mean 361 days, 0.99 years), and for placebo, the duration of follow-up ranged from 12 to 365 days (mean 354 days, 0.97 years). The results presented here for the ITT analysis are based on 514 participants (259 bisoprolol, 255 placebo) (see *Figure 4*). In total, there were 504.4 person years of follow-up data, with 256.7 person years in the bisoprolol group and 247.7 person years in placebo group (see *Table 10*).

Intention-to-treat analysis

Primary outcome: total number of exacerbations of chronic obstructive pulmonary disease requiring a change in management

In total, 199/259 (76.8%) of participants allocated to bisoprolol had at least 1 exacerbation, with 526 exacerbations in the group overall. For participants allocated to placebo, 197/255 (77.3%) had at least 1 exacerbation, and there were 513 exacerbations in the group overall. 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 IRR (bisoprolol vs. placebo) and 95% CI for exacerbation was 0.97 (0.84 to 1.13), indicating no difference in the exacerbation rate during the 12-month follow-up period for those on bisoprolol compared with placebo (see *Table 10*).

Secondary outcome: time to the first exacerbation of chronic obstructive pulmonary disease

To enable comparisons with the BLOCK COPD trial, we also conducted an analysis of time to the first exacerbation of COPD after randomisation (the primary outcome of the BLOCK COPD trial) (see *Table 10*). There was no significant difference between the two treatment groups in the median (IQR) time until the first exacerbation, which was 96.0 (27.0–172.5) days for participants allocated to bisoprolol and 70.0 (27.0–160.0) days for participants allocated to placebo. In a Cox regression analysis, the adjusted HR (95% CI) comparing bisoprolol with placebo for time to first exacerbation was 0.94 (0.78 to 1.16), suggesting no significant difference between the treatment groups in terms of time to first exacerbation (from point of randomisation) during the 12-month follow-up period.

Secondary outcome: total number of exacerbations of chronic obstructive pulmonary disease resulting in hospital admission

Of the 259 participants allocated to bisoprolol, 52 (20.1%) had at least 1 exacerbation of COPD requiring hospital admission, with 71 hospital admissions in total for the group. For the 255 participants allocated to placebo, there were 50 (19.6%) participants with at least 1 COPD exacerbation requiring hospital admission and 68 admissions in total. A comparison of the proportion with at least one exacerbation requiring hospital admission was not statistically significant (20.1% bisoprolol vs. 19.6% placebo, $p = 0.894$). In the adjusted model, the IRR (95% CI) for exacerbations of COPD requiring hospital treatment was 1.00 (0.67 to 1.50), suggesting that bisoprolol resulted neither in a reduction nor an increase in the number of exacerbations requiring hospital admission when compared with placebo (*Table 11*).

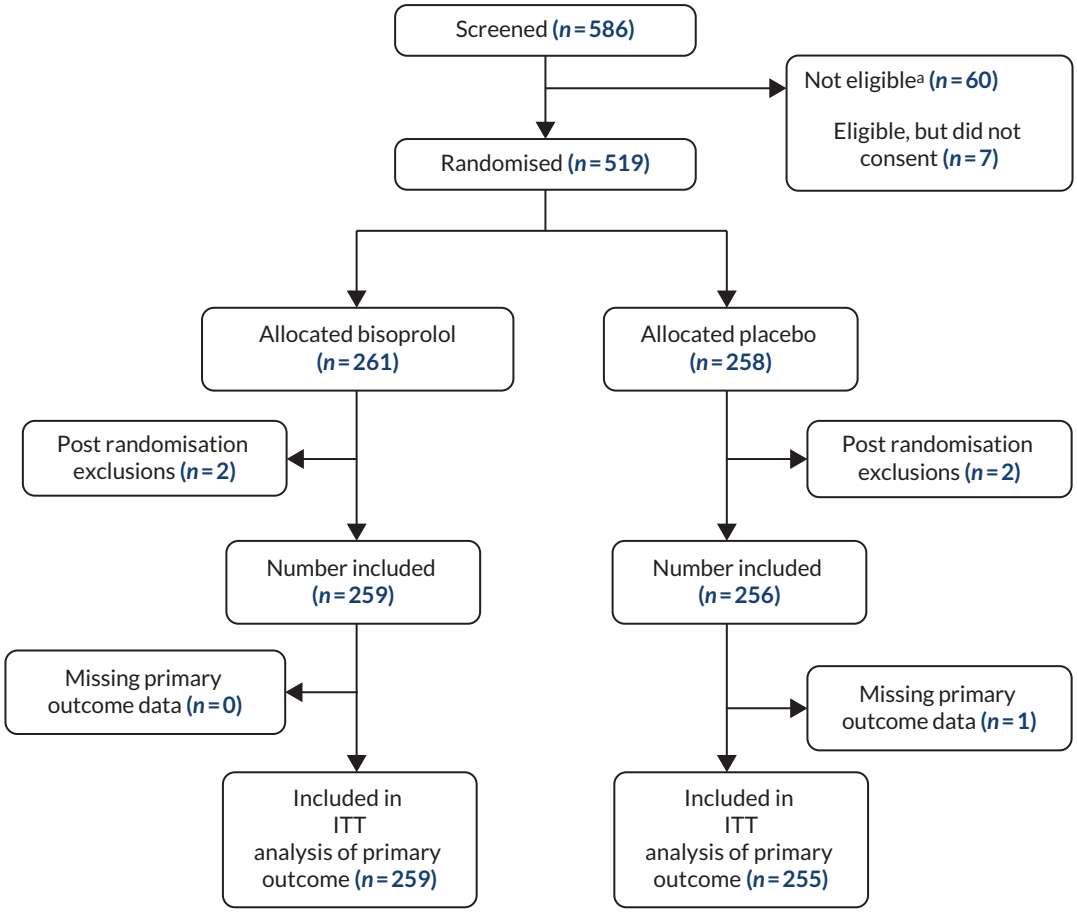

FIGURE 4 Diagram illustrating enrolment, randomisation and follow-up of participants. a, Reasons for ineligibility were as follows: 31 did not meet inclusion criteria for established COPD diagnosis or had predominant respiratory disease other than COPD, 4 had an asthma diagnosis before the age of 40, 5 had fewer than 2 exacerbations in previous year, 2 were prescribed contraindicated medication, 4 were not clinically stable, 6 had heart rate < 60/b.p.m., 2 had systolic blood pressure < 100 mmHg, one had a condition that was a guideline recommendation for beta-blocker therapy, 2 had conditions triggered by bisoprolol, and there was no information available for two.

TABLE 10 Primary exacerbation outcomes (ITT analysis) – 12 months

	Bisoprolol	Placebo		Estimate	Lower CI	Upper CI	*p*-value
Primary outcome: exacerbations							
Total number included in analysis	259	255					
Person years follow-up	256.7	247.7					
Number with at least one exacerbation	199	197					
Total number of exacerbations	526	513					
Mean number of exacerbations	2.03	2.01	Unadjusted IRR	0.99	0.84	1.16	0.874
SD (number of exacerbations)	1.91	1.75	Adjusted IRR[a]	0.97	0.84	1.13	0.720
Time to first exacerbation (from randomisation) (a secondary outcome)							
Total number included in analysis	259	255					
Number with at least one exacerbation	199	197					
% with at least one exacerbation	76.83	77.25					
Median time to first exacerbation (days)	96.00	70.00					

TABLE 10 Primary exacerbation outcomes (ITT analysis) – 12 months (*continued*)

	Bisoprolol	Placebo		Estimate	Lower CI	Upper CI	*p*-value
25th percentile [time to first exacerbation (days)]	27.00	27.00	Unadjusted HR	0.94	0.77	1.15	0.556
75th percentile [time to first exacerbation (days)]	172.50	160.00	Adjusted HR[a]	0.94	0.78	1.16	0.598

a Adjusted for: centre (as a random effect), recruitment setting (primary or secondary care), age centred on the mean, sex (male/female), smoking status (current vs. ex), FEV_1% predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long-term antibiotics.

TABLE 11 Secondary outcome: exacerbations of COPD requiring hospital treatment (ITT analysis) – 12 months

	Bisoprolol	Placebo		Estimate	Lower CI	Upper CI	*p*-value
Exacerbations requiring hospital treatment							
Total number included in analysis	259	255					
Person years follow-up	256.7	247.7					
Number with at least one exacerbation	52	50					
Total number of exacerbations	71	68					
Mean number of exacerbations	0.27	0.27	Unadjusted IRR	1.06	0.70	1.62	0.771
SD (number of exacerbations)	0.63	0.65	Adjusted IRR[a]	1.00	0.67	1.50	0.992
Emergency hospital admissions (non-COPD)							
Total number included in analysis	259	255					
Number with at least one emergency hospital admission	36	28					
Total admissions	47	32					
Mean admission rate	0.18	0.12	Unadjusted IRR	1.46	0.86	2.49	0.162
SD admission rate	0.51	0.44	Adjusted IRR[a]	1.47	0.88	2.45	0.139

a Adjusted for: centre (as a random effect), recruitment setting (primary or secondary care), age centred on the mean, sex (male/female), smoking status (current vs. ex), FEV_1% predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long-term antibiotics.

Secondary outcome: total number of emergency hospital admissions (non-chronic obstructive pulmonary disease)

In the bisoprolol group, 36 (13.9%) participants had a total of 47 emergency hospital admission that were not COPD related, similarly 28 (11.0%) of the placebo group had a total of 32 non-COPD-related emergency admissions to hospital. The proportion of participants having one or more non-COPD-related emergency hospital admissions did not differ significantly between the two groups ($p = 0.316$) and the adjusted IRR (95% CI) was 1.47 (0.88 to 2.45), suggesting no significant difference in rate of emergency (unscheduled) hospital admissions between the groups (see *Table 11*).

Secondary outcome: mortality (all cause and chronic obstructive pulmonary disease/respiratory related)

There were 24 deaths (from all causes) during the 12-month follow-up period, 11 (4.3%) in participants allocated to bisoprolol and 13 (5.1%) in participants allocated to placebo. These deaths were COPD/respiratory related for two participants allocated to bisoprolol and nine for participants allocated to placebo. For bisoprolol relative to placebo, the adjusted HR (95% CI) for deaths from all causes was 0.77 (0.34 to 1.73), and for COPD/respiratory-related causes of death 0.19 (0.04 to 0.88), $p = 0.034$. Although there was evidence that bisoprolol was associated with significantly reduced COPD/respiratory-related mortality, this did not translate into a reduction in all-cause mortality (see *Table 12*).

Secondary outcome: total number of major adverse cardiovascular events

In total, there were six MACE reported during the follow-up, four of these occurred in three participants allocated to bisoprolol and two occurred in participants allocated to placebo (1.2% bisoprolol vs. 0.8% placebo). The unadjusted IRR (95% CI) was 1.01 (0.12 to 8.29), suggesting no significant difference in MACE between the groups (see *Table 12*).

Secondary outcome: lung function (% predicted forced expiratory volume in 1 second and forced vital capacity)

Lung function data from spirometry were available for 507 (98.4%) participants at baseline (256 bisoprolol, 251 placebo), 179 (34.8%) participants (92 bisoprolol, 87 placebo) after 6 months of treatment and for 51 (9.9%) participants (30 bisoprolol, 21 placebo) after 12 months of treatment (see *Table 13*). The notable reduction in the availability of spirometry at 6 and 12 months reflects the impact of COVID-19 and our inability to perform spirometry as outlined earlier. When expressed as a proportion of participants whose 6- or 12-month follow-up with spirometry took place before COVID-19, and were allowed to perform spirometry, the proportion of participants from whom we were able to obtain spirometry was 76% (179/235) at 6 months and 67% (51/76) at 12 months. In the ITT analysis, lung function was not found to differ significantly between the treatment groups. The overall difference in FEV_1 per cent predicted (across the 12-month period) was −4.53% (−10.22, 1.16) between the groups. A similar pattern was observed for per cent predicted FVC with a difference of −5.03% (−17.78, 7.73) (see *Table 13*).

To investigate the possible consequences of only 10% of the participants providing lung function data after 12 months, further exploratory analyses were conducted. At baseline, the mean FEV_1 per cent predicted of the 30 participants allocated to bisoprolol, for whom FEV_1 data were available at 12 months, was 49.9% (at 12 months 43.3%). At baseline, the mean FEV_1 per cent predicted of the 21 participants allocated to placebo, for whom FEV_1 data were available at 12 months, was 56.7% (at 12 months 53.1%). Similarly, for the 28 participants allocated to bisoprolol with FVC data at 12 months, the mean baseline FVC was 84.8% (80.7% at 12 months), and for the 20 participants allocated to placebo

TABLE 12 Secondary clinical outcomes (ITT analysis)

	Bisoprolol	Placebo		Estimate	Lower CI	Upper CI	*p*-value
All-cause mortality							
Total number included in analysis	259	255					
Number deceased within 12 months	11	13	Unadjusted HR	0.82	0.37	1.84	0.632
% deceased within 12 months	4.25	5.10	Adjusted HR[a]	0.77	0.34	1.73	0.526
COPD/respiratory-related mortality							
Total number included in analysis	259	255					
Number deceased within 12 months	2	9	Unadjusted HR	0.21	0.05	0.99	0.049
% deceased within 12 months	0.77	3.53	Adjusted HR[a]	0.19	0.04	0.88	0.034
Total number of MACEs							
Total number included in analysis	259	255					
Number with ≥ 1 MACE	3	2					
Total MACEs	4	2					
Mean MACE rate	0.02	0.01	Unadjusted IRR	1.01	0.12	8.29	0.994
SD MACE rate	0.16	0.09	Adjusted IRR[a]	NA	NA	NA	NA

a Adjusted for: centre (as a random effect), recruitment setting (primary or secondary care), age centred on the mean, sex (male/female), smoking status (current vs. ex), FEV_1% predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long-term antibiotics.

TABLE 13 Lung function (ITT analysis)

Outcome	Time point		Bisoprolol	Placebo		Overall mean difference[a]	Lower CI	Upper CI	*p*-value
% Predicted FEV_1	Baseline	*N*	256	251					
		Mean	49.31	51.30					
		SD	19.04	19.11					
	6 months	*N*	92	87					
		Mean	47.83	47.01	Unadjusted	0.44	−4.98	5.85	0.874
		SD	18.84	19.28	Adjusted[b]	−0.75	−3.61	2.10	0.606
	12 months	Total *N*	30	21					
		Mean	43.30	53.12	Unadjusted	−11.22	−22.30	−0.14	0.053
		SD	20.80	18.86	Adjusted[b]	−4.53	−10.22	1.16	0.129
% Predicted FVC	Baseline	*N*	254	248					
		Mean	92.58	84.69					
		SD	164.11	22.32					
	6 months	*N*	84	77					
		Mean	82.33	79.08	Unadjusted	2.50	−5.05	10.05	0.518
		SD	29.82	24.40	Adjusted[b]	0.74	−5.74	7.23	0.823
	12 months	*N*	28	20					
		Mean	80.65	86.75	Unadjusted	−8.84	−21.97	4.30	0.195
		SD	29.79	26.05	Adjusted[b]	−5.03	−17.78	7.73	0.446

a Mean difference represents overall mean difference between bisoprolol and placebo.
b Adjusted for: centre (as a random effect), recruitment setting (primary or secondary care), age centred on the mean, sex (male/female), smoking status (current vs. ex), FEV_1% predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long-term antibiotics.

with FVC data at 12 months, the mean baseline FVC was 92.0% (86.8% at 12 months). This analysis suggests that any differences in FEV_1 and FVC at 12 months between the two groups, for whom lung function data were available at 12 months (10%), were largely present at baseline.

Secondary outcome: Transition Dyspnoea Index

The TDI was used to quantify changes in the severity of breathlessness from the baseline as established by the BDI. *Tables 14* and *15* detail the total and individual TDI domain scores at 6 and 12 months for each treatment group. The mean total TDI scores at 6 and 12 months for each treatment group were negative, suggesting some deterioration in the symptom of breathlessness during the treatment period; however, the deterioration in breathlessness was statistically significantly greater in the participants allocated to bisoprolol adjusted mean difference at 12 months [−0.73 (−1.44, −0.01), $p = 0.047$]. Analysis of the individual TDI domains indicated that bisoprolol was associated with a statistically significant deterioration in the domain 'magnitude of task' [−0.29 (−0.55, −0.04), $p = 0.022$], suggesting that less physical tasks were causing breathlessness.[75,83]

Secondary outcome: chronic obstructive pulmonary disease assessment test, EuroQoL-5 Dimensions, five-level version

The CAT scores were very similar between the treatment groups at baseline (see *Table 16*) and declined for both groups during the 12-month treatment period (i.e. reduced impact of COPD on health and well-being). The CAT scores were significantly greater for the bisoprolol group at 6 months compared to placebo, adjusted mean difference (95% CI) 1.64 (0.05 to 3.23), $p = 0.044$;[88] however, there was no significant between-group difference in the CAT scores at the end of

TABLE 14 Change in breathlessness as quantified by TDI – total score (ITT analysis)

Outcome	Time point		Bisoprolol	Placebo		Mean difference[a]	Lower CI	Upper CI	*p*-value
Total score	6 months (TDI score)	*N*	199	198					
		Mean	−0.83	−0.34	Unadjusted	−0.59	−1.14	−0.04	0.035
		SD	2.78	2.91	Adjusted[b]	−0.62	−1.16	−0.07	0.028
	12 months (TDI score)	*N*	183	188					
		Mean	−1.73	−1.01	Unadjusted	−0.87	−1.59	−0.16	0.016
		SD	3.66	3.58	Adjusted[b]	−0.73	−1.44	−0.01	0.047

a Mean difference represents overall mean difference between bisoprolol and placebo.
b Adjusted for: centre (as a random effect), recruitment setting (primary or secondary care), age centred on the mean, sex (male/female), smoking status (current vs. ex), FEV_1% predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long-term antibiotics, baseline BDI.

TABLE 15 Change in breathlessness as quantified by TDI – individual domains (ITT analysis)

Outcome	Time point		Bisoprolol	Placebo		Mean difference[a]	Lower CI	Upper CI	*p*-value
Change in functional impairment	6 months (TDI score)	*N*	201	198					
		Mean	−0.24	−0.08	Unadjusted	−0.19	−0.39	0.02	0.078
		SD	1.05	1.06	Adjusted[b]	−0.20	−0.41	0.00	0.054
	12 months (TDI score)	*N*	183	189					
		Mean	−0.51	−0.29	Unadjusted	−0.26	−0.51	−0.01	0.039
		SD	1.28	1.24	Adjusted[b]	−0.22	−0.47	0.03	0.086
Change in magnitude of task	6 months (TDI score)	*N*	203	201					
		Mean	−0.29	−0.02	Unadjusted	−0.28	−0.47	−0.09	0.005
		SD	0.98	1.03	Adjusted[b]	−0.29	−0.49	−0.10	0.004
	12 months (TDI score)	*N*	185	190					
		Mean	−0.56	−0.26	Unadjusted	−0.33	−0.58	−0.08	0.010
		SD	1.30	1.21	Adjusted[b]	−0.29	−0.55	−0.04	0.022
Change in magnitude of effort	6 months (TDI score)	*N*	206	201					
		Mean	−0.31	−0.21	Unadjusted	−0.13	−0.34	0.08	0.230
		SD	1.09	1.12	Adjusted[b]	−0.13	−0.34	0.08	0.227
	12 months (TDI score)	*N*	185	191					
		Mean	−0.66	−0.46	Unadjusted	−0.26	−0.52	−0.00	0.049
		SD	1.33	1.34	Adjusted[b]	−0.20	−0.46	0.06	0.141

a Mean difference represents overall mean difference between bisoprolol and placebo.
b Adjusted for: centre (as a random effect), recruitment setting (primary or secondary care), age centred on the mean, sex (male/female), smoking status (current vs. ex), FEV_1% predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long-term antibiotics, baseline BDI.

TABLE 16 Patient-reported outcomes – CAT score (ITT analysis)

Outcome, time point		Bisoprolol	Placebo		Overall mean difference[a]	Lower CI	Upper CI	*p*-value
CAT score								
Baseline	*N*	259	255					
	Mean	22.74	22.01					
	SD	8.12	8.04					
6 months	*N*	219	222					
	Mean	20.29	18.73	Unadjusted	1.91	0.25	3.57	0.024
	SD	8.85	9.25	Adjusted[b]	1.64	0.05	3.23	0.044
12 months	*N*	207	202					
	Mean	19.43	19.77	Unadjusted	0.04	−1.69	1.77	0.962
	SD	8.86	9.40	Adjusted[b]	−0.59	−2.26	1.07	0.485

a Mean difference represents overall mean difference between bisoprolol and placebo.
b Adjusted for: centre (as a random effect), recruitment setting (primary or secondary care), age centred on the mean, sex (male/female), smoking status (current vs. ex), FEV_1% predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long-term antibiotics.

the 12-month treatment period, mean difference −0.59 (−2.26, 1.07). Overall, it appears that there was no significant difference between the groups on the impact of COPD on the participants' overall health and well-being.

EuroQoL-5 Dimensions, five-level version utility scores were balanced between the two treatment groups at baseline, and there was very little change during the 12-month treatment period and no significant differences between the two treatment groups (see *Table 17*). Responses to individual questions on the EQ-5D-5L are presented in *Appendix 4*. The EQ-5D-5L visual analogue scale (VAS) scores of the participants allocated to bisoprolol and placebo were balanced at baseline; although, the VAS scores of the participants allocated to bisoprolol were lower at the 6-month time point [mean difference −4.56 (−8.64, −0.47)], there were no significant differences at the end of the 12-month treatment period.[89]

Safety outcomes (safety population)

The safety population comprised all participants who were randomised and included in the study who initiated their study medication. In total, 4/259 (1.5%) of participants allocated to bisoprolol and 4/256 (1.6%) allocated to placebo did not initiate study treatment and 1 participant was lost to follow-up very soon after randomisation. The safety population consisted of 506 (98.3%) participants (255 bisoprolol, 251 placebo).

Serious adverse events

In total, 84 SAEs were reported in BICS – 6 initially as possible serious adverse reactions (SARs) and 78 as SAEs. The final outcome in 23 of these was fatal.

The six events reported as possible SARs within BICS are described in *Appendix 5*. For two of these, the event was assessed to be 'expected' on the basis of the information contained within the Reference Safety Information, so were considered as an expected SAR until the end of the study when they were unblinded. Both were allocated to placebo, so have been described as SAEs in this report. The other four events were assessed as unexpected and were therefore unblinded at the time of the event – two had been allocated to bisoprolol and were reported to the sponsor, MHRA and REC as SUSARs. The other two events had been allocated to placebo, and so have been described as SAEs in this report.

Both SUSARs involved falls. The first was a fall resulting in fracture of base of neck of femur (SOC injury, poisoning and procedural complications); the other was postural drop leading to fall and right wrist injury (SOC vascular disorders).

TABLE 17 Patient-reported outcomes – EQ-5D-5L (ITT analysis)

Outcome, time point		Bisoprolol	Placebo		Overall mean difference[a]	Lower CI	Upper CI	*p*-value
EQ-5D-5L utility								
Baseline	*N*	256	251					
	Mean	0.59	0.59					
	SD	0.26	0.25					
6 months	*N*	208	208					
	Mean	0.59	0.62	Unadjusted	−0.04	−0.09	0.01	0.110
	SD	0.26	0.26	Adjusted[b]	−0.03	−0.08	0.01	0.185
12 months	*N*	196	195					
	Mean	0.61	0.61	Unadjusted	0.00	−0.05	0.05	0.952
	SD	0.26	0.26	Adjusted[b]	0.02	−0.03	0.06	0.491
EQ-5D-5L VAS								
Baseline	*N*	257	252					
	Mean	61.39	61.02					
	SD	21.26	20.69					
6 months	*N*	206	208					
	Mean	58.89	62.44	Unadjusted	−4.37	−8.53	−0.22	0.040
	SD	23.20	20.98	Adjusted[b]	−4.56	−8.64	−0.47	0.029
12 months	*N*	194	195					
	Mean	59.41	60.05	Unadjusted	−0.88	−5.00	3.24	0.677
	SD	21.12	20.69	Adjusted[b]	−0.77	−4.89	3.35	0.713

a Mean difference represents overall mean difference between bisoprolol and placebo.
b Adjusted for: centre (as a random effect), recruitment setting (primary or secondary care), age centred on the mean, sex (male/female), smoking status (current vs. ex), FEV_1% predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long-term antibiotics.

The 82 events finally classified as SAEs within BICS are described in *Table 18*: 45 were in the bisoprolol group and 37 in the placebo group. Although not within the safety population, for the sake of completeness we note that two SAEs were reported by participants who failed to initiate study treatment: one was musculoskeletal chest pain in a participant allocated to placebo and the other was a bowel obstruction in a participant allocated to bisoprolol.

When classified by MedDRA SOC code, the most common type of SAE was 'infections and infestations' that occurred in 16 participants (10 bisoprolol, 6 placebo) and comprised cases of pneumonia, urinary sepsis, influenza and COVID-19. SAEs with a coding of 'respiratory, thoracic and mediastinal' occurred in 15 participants (4 bisoprolol, 11 placebo); the majority of these SAEs were participants whose death was attributed to COPD. The coding 'neoplasms benign, malignant and unspecified' occurred in 11 participants (4 bisoprolol, 7 placebo). A similar number of SAEs were coded 'cardiac disorders' (7 bisoprolol, 3 placebo) and comprised arrhythmias and acute coronary syndromes. Although SAE-coded 'gastrointestinal disorders' were reported more frequently by participants allocated to bisoprolol (seven bisoprolol, two placebo), this difference was not statistically significant and no single diagnosis predominated, and in one case the participant had not initiated bisoprolol. No pregnancies were reported. Line listings are provided in *Appendix 6*.

Table 18 summarises the SOC classification for the 82 SAEs within BICS (78 reported as SAEs and 4 reported initially as SARs but reclassified as SAEs after unblinding).

TABLE 18 Summary of MedDRA SOC classification of SAEs

MedDRA SOC classification	Bisoprolol (*N* = 259)	Placebo (*N* = 255)
Respiratory, thoracic and mediastinal disorders (*n*)	4	11
Neoplasms benign, malignant and unspecified (*n*)	4	7
Musculoskeletal and connective tissue disorders (*n*)	0	1[a]
Cardiac disorders (*n*)	7	3
Vascular disorders (*n*)	0	2
Nervous system disorders (*n*)	4	2
Gastrointestinal disorders (*n*)	7[b]	2
Infections and infestations (*n*)	10	6
Blood and lymphatic system disorders (*n*)	0	1
Psychiatric disorders (*n*)	1	1
Injury, poisoning and procedural complications (*n*)	5	1
General disorders and administration site conditions (*n*)	1	0
Metabolism and nutrition disorders (*n*)	1	0
Renal and urinary disorders (*n*)	1	0
Total	45	37

a Failed to initiate study treatment.
b One failed to initiate study treatment.

Adverse reactions

Information on ARs was available for 506 of the participants (255 bisoprolol, 251 placebo), with 306 (60.5%) suffering at least one AR during the 52-week treatment period [149 bisoprolol, 157 placebo, relative risk (RR) (95% CI) 0.93 (0.81 to 1.08) $p = 0.392$]. There were 1233 ARs in total, with 601 in those allocated to bisoprolol and 632 in those allocated placebo. *Table 19* presents these ARs in more detail, with number (and percentage) of participants with at least one AR of that type and total number of ARs of that type. The five most common ARs were classified as 'general disorders' (including asthenia, fatigue) [23.9% bisoprolol, 27.5% placebo, RR (95% CI) 0.87 (0.65 to 1.17) $p = 0.414$], 'nervous system' (dizziness, headaches) [22.0% bisoprolol, 23.1% placebo, RR (95% CI) 0.95 (0.69 to 1.31) $p = 0.840$], 'gastrointestinal disorders' (nausea, diarrhoea, constipation) [20.0% bisoprolol, 21.1% placebo, RR (95% CI) 0.95 (0.67 to 1.33) $p = 0.841$], 'musculoskeletal' (muscle weakness/cramps) [20.0% bisoprolol, 21.1% placebo, RR (95% CI) 0.95 (0.67 to 1.33) $p = 0.841$] and 'psychiatric disorders' (nightmares, depression) [16.9% bisoprolol, 20.3% placebo, RR (95% CI) 0.83 (0.58 to 1.20) $p = 0.376$]. 'Vascular disorders' (hypotension, cold peripheries) were more common in those allocated to bisoprolol/placebo [20.8% bisoprolol, 12.8% placebo, RR (95% CI) 1.63 (1.09 to 2.44) $p = 0.022$]. The proportion of participants reporting respiratory ARs was similar in those allocated to bisoprolol (9.8%) and placebo (12.3%), RR (95% CI) 0.79 (0.48 to 1.31) $p = 0.441$. Apart from the excess of 'vascular disorders' (hypotension, cold peripheries), there were no other observed significant differences in ARs between treatment groups.

Subgroup analysis (intention to treat)

Figure 5 summarises the results of the subgroup analysis for the pre-specified subgroups with the *p*-value for the interaction in the adjusted model (the data are also provided in *Appendix 7*). There was no evidence that any effect of bisoprolol differed between subgroups of gender, age, smoking status, BMI, baseline COPD treatments, exacerbation history, GOLD COPD classification, use of maintenance oral corticosteroids, BDI or dose of bisoprolol.

In further subgroup analysis, the possible consequences of the COVID-19 pandemic on the primary exacerbation outcome were investigated because of the impact of shielding advice on the incidence of COPD exacerbation (see *Table 20*). A total of 90 participants had been randomised and completed their follow-up before people with COPD

TABLE 19 Adverse reactions (safety population)

	Bisoprolol	Placebo	RR (95% CI)	*p*-value
Total number included in analysis	255	251		
Number of participants with at least one AR	149	157		
% of participants with at least one AR	58.4	62.6	0.93 (0.81 to 1.08)	0.392
Total number of ARs	601	632		
Blood and lymphatic system disorders				
N of participants with at least one AR of this type	1	2		
% of participants with at least one AR of this type	0.39	0.79	0.49 (0.04 to 5.39)	0.989
Total number of ARs of this type	1	2		
Cardiac disorders				
N of participants with at least one AR of this type	5	8		
% of participants with at least one AR of this type	1.96	3.19	0.62 (0.20 to 1.85)	0.555
Total number of ARs of this type	5	8		
Ear and labyrinth disorders				
N of participants with at least one AR of this type	14	21		
% of participants with at least one AR of this type	5.49	8.37	0.66 (0.34 to 1.26)	0.271
Total number of ARs of this type	15	24		
Endocrine disorders				
N of participants with at least one AR of this type	0	1		
% of participants with at least one AR of this type	0	0.40	NA	NA
Total number of ARs of this type	0	1		
Eye disorders				
N of participants with at least one AR of this type	19	20		
% of participants with at least one AR of this type	7.45	7.97	0.94 (0.51 to 1.71)	0.959
Total number of ARs of this type	21	25		
Gastrointestinal disorders				
N of participants with at least one AR of this type	51	53		
% of participants with at least one AR of this type	20.1	21.1	0.95 (0.67 to 1.33)	0.841
Total number of ARs of this type	77	75		
General disorders and administration site conditions				
N of participants with at least one AR of this type	61	69		
% of participants with at least one AR of this type	23.9	27.5	0.87 (0.65 to 1.17)	0.414
Total number of ARs of this type	85	99		
Hepatobiliary disorders				
N of participants with at least one AR of this type	2	0		
% of participants with at least one AR of this type	0.78	0	NA	NA
Total number of ARs of this type	2	0		

TABLE 19 Adverse reactions (safety population) (*continued*)

	Bisoprolol	Placebo	RR (95% CI)	*p*-value
Infections and infestations				
N of participants with at least one AR of this type	1	2		
% of participants with at least one AR of this type	0.39	0.80	NA	NA
Total number of ARs of this type	1	2		
Injury, poisoning and procedural complications				
N of participants with at least one AR of this type	2	1		
% of participants with at least one AR of this type	0.78	0.40	NA	NA
Total number of ARs of this type	2	1		
Investigations				
N of participants with at least one AR of this type	1	2		
% of participants with at least one AR of this type	0.39	0.80	NA	NA
Total number of ARs of this type	1	2		
Musculoskeletal and connective tissue disorders				
N of participants with at least one AR of this type	51	54		
% of participants with at least one AR of this type	20	21.1	0.95 (0.67 to 1.33)	0.841
Total number of ARs of this type	65	62		
Neoplasms benign, malignant and unspecified (including cysts and polyps)				
N of participants with at least one AR of this type	1	0		
% of participants with at least one AR of this type	0.4	0	NA	NA
Total number of ARs of this type	1	0		
Nervous system disorders				
N of participants with at least one AR of this type	56	58		
% of participants with at least one AR of this type	22.0	23.1	0.95 (0.69 to 1.31)	0.840
Total number of ARs of this type	87	95		
Psychiatric disorders				
N of participants with at least one AR of this type	43	51		
% of participants with at least one AR of this type	16.9	20.3	0.83 (0.58 to 1.20)	0.376
Total number of ARs of this type	72	80		
Renal and urinary disorders				
N of participants with at least one AR of this type	1	2		
% of participants with at least one AR of this type	0.39	0.8	NA	NA
Total number of ARs of this type	1	2		
Reproductive system and breast disorders				
N of participants with at least one AR of this type	5	5		
% of participants with at least one AR of this type	1.96	1.99	NA	NA

continued

TABLE 19 Adverse reactions (safety population) (*continued*)

	Bisoprolol	Placebo	RR (95% CI)	*p*-value
Total number of ARs of this type	5	5		
Respiratory, thoracic and mediastinal disorders				
N of participants with at least one AR of this type	25	31		
% of participants with at least one AR of this type	9.8	12.3	0.79 (0.48 to 1.31)	0.441
Total number of ARs of this type	28	34		
Skin and subcutaneous tissue disorders				
N of participants with at least one AR of this type	34	35		
% of participants with at least one AR of this type	13.3	13.9	0.96 (0.62 to 1.48)	0.944
Total number of ARs of this type	41	38		
Vascular disorders				
N of participants with at least one AR of this type	53	32		
% of participants with at least one AR of this type	20.8	12.8	1.63 (1.09 to 2.44)	0.022
Total number of ARs of this type	64	41		

were advised to shield because of COVID-19 (pre-22 March 2020), and 90 participants were randomised after the advice to shield was withdrawn (post-1 August 2021). The majority of participants (*n* = 334) were randomised before the shielding advice and had a varying proportion of their treatment periods during the period when shielding was advised (22 March 2020 to 31 July 2021).

For participants with their treatment periods entirely pre-shielding or whose treatment period was during shielding, the mean (SD) number of exacerbations per participant per year were similar and the adjusted IRRs indicated no difference in the exacerbation rates during the 12-month follow-up period for those on bisoprolol compared with placebo (see *Table 20*): pre-shielding adjusted IRR (95% CI) 0.99 (0.69 to 1.43), shielding 1.01 (0.84 to 1.21). Although the mean number of exacerbations per participant per year was about 30% lower for participants randomised after shielding, there was no significant difference between treatment groups, adjusted IRR (95% CI) 0.82 (0.55 to 1.23). The conclusion of this subgroup analysis was that although the COVID-19 pandemic and shielding appeared to be associated with a reduction in the absolute incidence of COPD exacerbation, there was no evidence that the COVID-19 pandemic and shielding affected any treatment effect of bisoprolol on COPD exacerbations.

Treatment adherence/compliance

Adherence/compliance was defined as participants having taken ≥ 70% of expected doses of study tablets. Of those randomised (*n* = 515), there were 357 (69.3%) participants (174 bisoprolol, 183 placebo) who fulfilled the definition of adherent/compliant (and make up the per-protocol population; see *Table 21*).

Within the bisoprolol group 85/259 (32.8%) were classed as non-adherent/non-compliant, with 4 of these never initiating treatment and 8 who persisted with study medication but reported that they were non-adherent/non-compliant (see *Table 21*). A total of 73 (28.2%) participants allocated to bisoprolol were non-persistent (i.e. actively ceased taking study medication), 42 were fixed on zero tablets during dose titration and 31 ceased sometime after dose titration but before 12 months. Within the placebo group, 73/256 (28.5%) were classed as non-adherent/non-compliant, with 4 never initiating medication and 6 who persisted with study medication, but reported that they were non-adherent/non-compliant (see *Table 21*). A total of 63 (24.6%) participants allocated to placebo were non-persistent

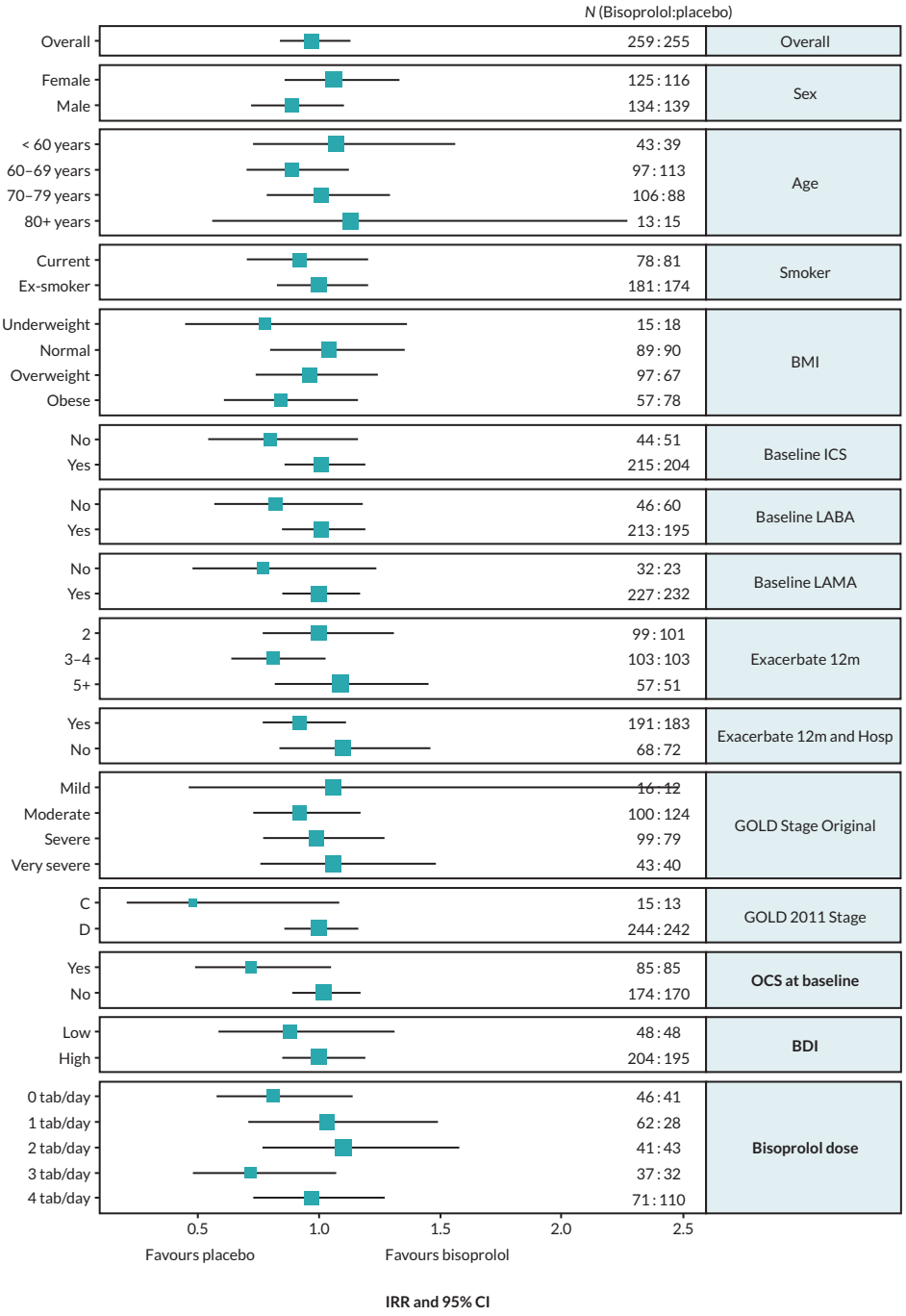

FIGURE 5 Forest plot of estimates from the subgroups. Adjusted for: centre (as a random effect), recruitment setting (primary or secondary care), age centred on the mean, sex (male/female), smoking status (current vs. ex), FEV_1% predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long-term antibiotics. GOLD, Global Initiative for Chronic Obstructive Lung Disease,[1] OCS, oral corticosteroid; 'exacerbate 12 m', exacerbations in previous 12 months; 'exacerbate 12 m and Hosp', exacerbations in previous 12 months resulting in hospitalisation; 'GOLD Stage Original', GOLD stage based on FEV_1.

with study medication, 38 were fixed on zero tablets (i.e. ceased) during dose titration and 25 ceased sometime after dose titration but before 12 months.

A comparison of the proportion non-adherent/compliant (32.8% bisoprolol vs. 28.2% placebo) was not significant (p = 0.259). In total, 73 of 259 participants in the placebo arm were non-persistent with medication compared to 62 of 256 in the placebo arm [unadjusted IRR = 1.16 (0.89, 1.51)]. Of the 136 participants who were non-persistent, 59% ceased during dose titration.

TABLE 20 Primary outcome (ITT analysis) – 12 months considering different periods before, during and after the COVID-19 pandemic

		Bisoprolol (*N* = 259)	Placebo (*N* = 255)		Estimate	Lower CI	Upper CI	*p*-value
Primary outcome: exacerbations requiring change in management								
Pre-shielding[a]	*N*	46	44					
	Mean	1.96	2.09					
	SD	2.01	1.72	Adjusted IRR[b]	0.99	0.69	1.43	0.953
Shielding[a]	*N*	167	167					
	Mean	2.17	2.14					
	SD	1.96	1.81	Adjusted IRR[b]	1.01	0.84	1.21	0.920
Post-shielding[a]	*N*	46	44					
	Mean	1.59	1.43					
	SD	1.53	1.42	Adjusted IRR[b]	0.82	0.55	1.23	0.341

a Pre-shielding: participants with the date of last follow-up before 22 March 2020; Shielding: participants randomised between 22 March 2019 and 22 March 2020 with the date of last follow-up between 22 March 2020 and 31 July 2021; Post-shielding: participants randomised after 1 August 2021.
Model included treatment arm, period and two-way interaction effect of treatment and period.
b Adjusted for: centre (as a random effect), recruitment setting (primary or secondary care), age centred on the mean, sex (male/female), smoking status (current vs. ex), FEV_1% predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long-term antibiotics.

TABLE 21 Compliance information

	Bisoprolol	Placebo
Total *N*	259	256
Not adherent/non-compliant (< 70%)[a]	85	73
Did not start medication (non-initiation)	4	4
Actively ceased medication (non-persistence)	73	63
Ceased during titration	42	38
Ceased after titration	31	25
Did not cease (persistent), but adherence/compliance < 70%	8	6
Adherent/compliant (> 70%)	174	183

a Unadjusted IRR 1.16, 95% CI 0.89 to 1.51, $p = 0.261$.

Reasons for stopping medication

Table 22 presents the reasons for stopping medication among the ITT population by MedDRA SOC. Most (59%) of the 136 participants who ceased study medication did so during the dose-titration period when the algorithm (based on intolerable side effects, heart rate, blood pressure or lung function) resulted in participants being 'fixed' on zero tablets a day. Using MedDRA SOC codes, the most common reasons for stopping medication were respiratory (usually exacerbations) (4.6% bisoprolol, 6.3% placebo), general (asthenia/fatigue) (4.2% bisoprolol, 6.3% placebo), cardiac (bradycardia) (3.9% bisoprolol, 2.0% placebo) and vascular (hypotension, cold peripheries) (2.7% bisoprolol, 0.4% placebo). As expected, more participants allocated to bisoprolol ceased study medication because of bradycardia, hypotension and cold peripheries; however, there was no evidence of participants allocated to bisoprolol being more likely to cease study medication because of respiratory issues.

TABLE 22 Reasons for stopping medication (of those randomised)

	Bisoprolol	Placebo
Total *N*	259	256
Actively ceased medication (non-persistent)	73	63
Ceased during titration (titrated to zero tablets)	42	38
Ceased after titration	31	25
Reason for stopping medication (MedDRA SOC) n (%)		
Cardiac disorders	10 (3.9%)	5 (2.0%)
Gastrointestinal disorders	8 (3.1%)	2 (0.8%)
General disorders and administration site conditions	11 (4.2%)	16 (6.3%)
Infections and infestations	2 (0.8%)	2 (0.8%)
Injury, poisoning and procedural complications	1 (0.4%)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	3 (1.2%)
Nervous system disorders	1 (0.4%)	0
Psychiatric disorders	0	1 (0.4%)
Respiratory, thoracic and mediastinal disorders	12 (4.6%)	16 (6.3%)
Skin and subcutaneous tissue disorders	2 (0.8%)	2 (0.8%)
Social circumstances	5 (1.9%)	7 (2.7%)
Surgical and medical procedures	1 (0.4%)	1 (0.4%)
Vascular disorders	7 (2.7%)	1 (0.4%)
Felt no benefit[a]	3 (1.2%)	1 (0.4%)
No reason given	10 (3.9%)	6 (2.3%)

a This is not a MedDRA SOC but included because it reflects the reason given for ceasing medication.

Vital signs

Heart rate and blood pressure data were available for all participants at baseline, 280 (54.4%) participants (141 bisoprolol, 139 placebo) after 6 months of treatment and for 147 (28.5%) participants (74 bisoprolol, 73 placebo) after 12 months of treatment (see *Table 23*). The reduction in the availability of these vital signs at 6 and 12 months reflects the impact of COVID-19 and our inability to perform face-to-face visits, and it should be noted that when compared with spirometry data, more vital sign data were available at 6 and 12 months because participants recruited after 31 July 2023 (*n* = 90) were provided with a digital sphygmomanometer. Heart rate, systolic and diastolic blood pressures were slightly lower in the bisoprolol group at 6 and 12 months.

Per-protocol analysis

The per-protocol population comprised the 357 (69.3%) participants of the ITT population that met the study definition of adherent with their study medication, that is taking ≥ 70% of their expected doses of study medication. The per-protocol analysis comprised 174 participants allocated to bisoprolol and 183 allocated to placebo (*Figure 6*).

TABLE 23 Vital signs in the two treatment groups at baseline, 6 and 12 months

	Bisoprolol				Placebo			
	N	Heart rate (/b.p.m.)	SBP (mmHg)	DBP (mmHg)	*N*	Heart rate (/b.p.m.)	SBP (mmHg)	DBP (mmHg)
Baseline								
Mean	259	77	132	76	256	80	133	78
SD		15.4	24	13.9		13.7	21.3	12.5
6 months								
Mean	141	75	131	76	139	79	132	77
SD		15.5	23.8	14.2		13.9	21.8	13.0
12 months								
Mean	74	74	128	74	73	79	131	76
SD		16.1	28.6	16.4		14.3	23.5	14.1

DBP, diastolic blood pressure; SBP, systolic blood pressure.

Primary outcome: total number of exacerbations of chronic obstructive pulmonary disease requiring a change in management

The per-protocol population comprised 353.4 years of follow-up data, with 172.3 person years in the bisoprolol group and 181.2 person years in placebo group (see *Table 24*). In total, 134/174 (77.0%) of participants allocated to bisoprolol had at least 1 exacerbation, with 351 exacerbations in the group overall. For participants allocated to placebo, 139/183 (76.0%) had at least 1 exacerbation, and there were 341 exacerbations in the group overall. The mean (SD) number of exacerbations per participant was 2.02 (1.90) in those allocated to bisoprolol and 1.86 (1.64) in those allocated to placebo. The adjusted IRR (bisoprolol vs. placebo) and 95% CI for exacerbation was 1.05 (0.88 to 1.27), indicating no difference in the exacerbation rate during the 12-month follow-up period for those on bisoprolol compared with placebo who were adherent/compliant with study medication (see *Table 24*).

Secondary outcome: time to first exacerbation of chronic obstructive pulmonary disease

In those allocated to and compliant with bisoprolol, the median time to first exacerbation of COPD was 111 days after randomisation. For those adherent/compliant with placebo, the median time to first exacerbation of COPD was 95.0 days. In a Cox regression analysis, the per-protocol adjusted HR for time to first exacerbation was 1.07 (0.84, 1.37), suggesting no difference between the treatment groups in terms of time to first exacerbation (from point of randomisation) during the 12-month follow-up period (see *Table 24*).

Secondary outcome: total number of exacerbations of chronic obstructive pulmonary disease resulting in hospital admission

In the per-protocol population, 29/174 (16.7%) participants allocated to bisoprolol had at least one COPD exacerbation requiring hospital admission, and there were 37 admissions in the group overall. In those allocated to placebo, 29/183 (15.8%) had at least 1 admission, with 38 admissions overall. The mean (SD) number of COPD exacerbations requiring hospital admission was 0.21 (0.54) for the 174 bisoprolol-adherent/compliant participants and 0.21 (0.58) for the 183 placebo-adherent/compliant participants. In the adjusted model, the IRR for COPD exacerbations requiring hospital admission was 1.06 (0.62, 1.82), suggesting no difference in the number of exacerbations requiring hospital admission for the bisoprolol-adherent/compliant group compared to placebo (see *Table 25*).

Secondary outcome: total number of emergency hospital admissions (non-chronic obstructive pulmonary disease)

In the per-protocol population, 36 participants had at least 1 admission to hospital with a non-COPD diagnosis (18 bisoprolol, 18 placebo); for bisoprolol-adherent/compliant participants, there were 22 admissions in total, and for placebo-adherent/compliant participants, there were 18 admissions in total. The adjusted IRR for admission was

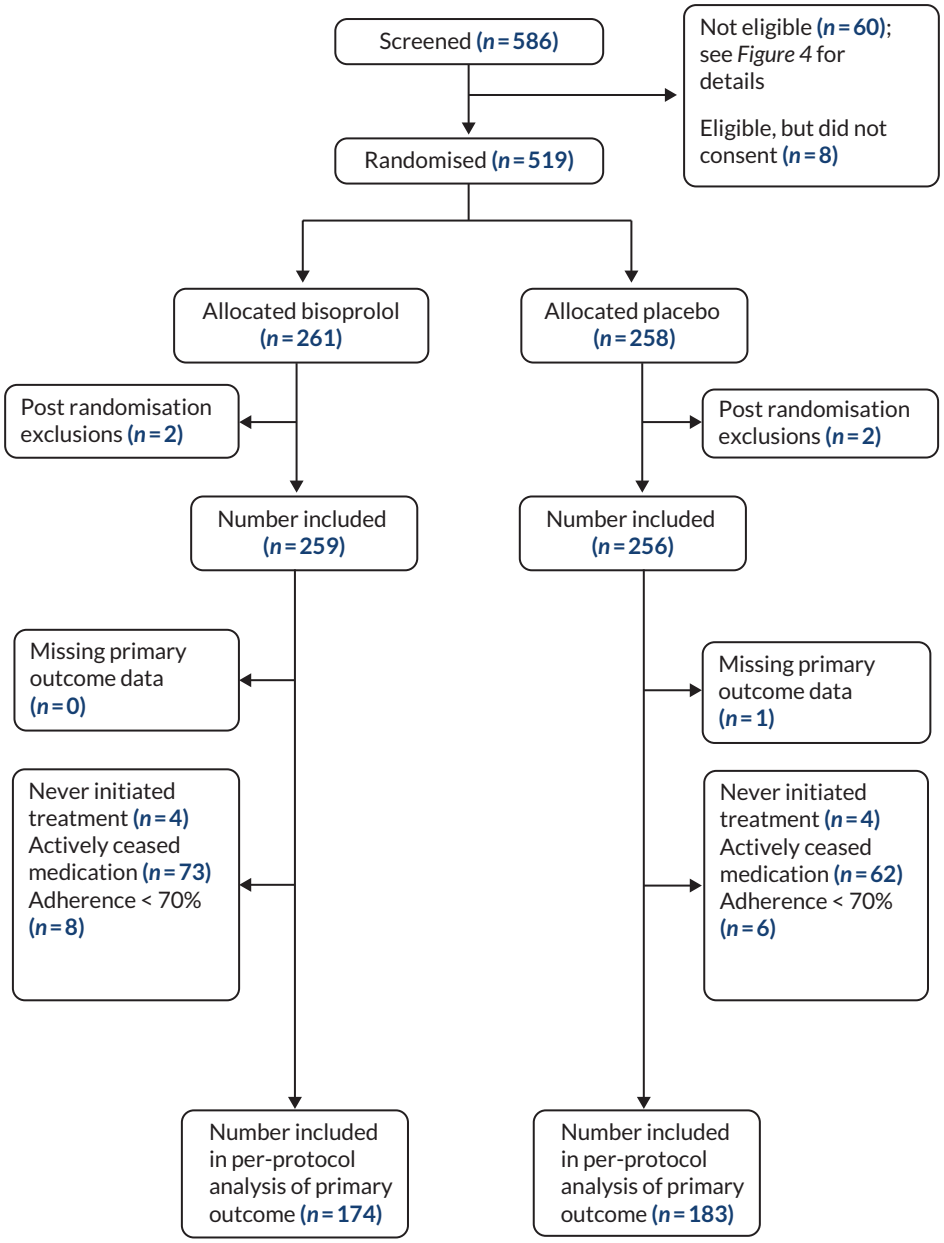

FIGURE 6 Consolidated Standards of Reporting Trials diagram (per-protocol analysis).

1.22 (0.64, 2.32), suggesting no significant difference in the rate of non-COPD emergency hospital admissions for participants adherent/compliant with bisoprolol compared to placebo (see *Table 25*).

Secondary outcome: mortality (all cause and chronic obstructive pulmonary disease/respiratory related)

There were 16 deaths (from all causes) during the 12-month follow-up period in the per-protocol population, 8 (4.6%) in participants adherent/compliant with bisoprolol and 8 (4.4%) in participants adherent/compliant with placebo. These deaths were COPD/respiratory related for 2 (1.15%) participants in the bisoprolol group and for 6 (3.28%) participants in the placebo group. For bisoprolol relative to placebo, the adjusted HR (95% CI) for deaths from all causes was 0.94 (0.35 to 2.51), and for COPD/respiratory-related causes, 0.33 (0.07 to 1.66) (see *Table 26*). Therefore, there was no evidence of a significant difference between treatment groups for mortality outcomes in the per-protocol population.

TABLE 24 Primary exacerbation outcomes (per-protocol analysis) – 12 months

	Bisoprolol	Placebo		Estimate	Lower CI	Upper CI	*p*-value
Primary outcome: exacerbations							
Total number included in analysis	174	183					
Person years follow-up	172.3	181.2					
Number (%) with at least one exacerbation	134 (77.0)	139 (76.0)					
Total number of exacerbations	351	341					
Mean number of exacerbations	2.02	1.86	Unadjusted IRR	1.08	0.89	1.30	0.460
SD (number of exacerbations)	1.90	1.64	Adjusted IRR[a]	1.05	0.88	1.27	0.582
Time to first exacerbation (from randomisation) (a secondary outcome)							
Total number included in analysis	174	183					
Number with at least one exacerbation	134	139					
Median time to first exacerbation (days)	111.00	95.00					
25th percentile [time to first exacerbation (days)]	32.50	37.00	Unadjusted HR	1.01	0.80	1.29	0.918
75th percentile [time to first exacerbation (days)]	172.75	176.50	Adjusted HR[a]	1.07	0.84	1.37	0.578

a Adjusted for: centre (as a random effect), recruitment setting (primary or secondary care), age centred on the mean, sex (male/female), smoking status (current vs. ex), FEV_1% predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long-term antibiotics.

TABLE 25 Secondary outcome: exacerbations of COPD requiring hospital treatment (per-protocol analysis) – 12 months

	Bisoprolol	Placebo		Estimate	Lower CI	Upper CI	*p*-value
Exacerbations requiring hospital treatment							
Total number included in analysis	174	183					
Number with at least one exacerbation	29	29					
Total number of exacerbations	37	38					
Mean number of exacerbations	0.21	0.21	Unadjusted IRR	1.00	0.57	1.75	0.989
SD (number of exacerbations)	0.54	0.58	Adjusted IRR[a]	1.06	0.62	1.82	0.833
Emergency hospital admissions (non-COPD)							
Total number included in analysis	174	183					
Number with at least one emergency hospital admission	18	18					
Total admissions	22	18					
Mean admission rate	0.13	0.10	Unadjusted IRR	1.29	0.66	2.51	0.461
SD admission rate	0.41	0.30	Adjusted IRR[a]	1.22	0.64	2.32	0.541

a Adjusted for: centre (as a random effect), recruitment setting (primary or secondary care), age centred on the mean, sex (male/female), smoking status (current vs. ex), FEV_1% predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long-term antibiotics.

Secondary outcome: total number of major adverse cardiovascular events

In total, there were three MACE reported during the follow-up in the per-protocol population, one of these occurred in a participants allocated to bisoprolol and two occurred in two participants allocated to placebo (0.57% bisoprolol vs. 1.09% placebo). The unadjusted IRR (95% CI) was 0.54 (0.10 to 2.84), suggesting no significant difference in MACE between the groups in the per-protocol analysis (see *Table 26*).

TABLE 26 Secondary clinical outcomes (per-protocol analysis)

	Bisoprolol	Placebo		Estimate	Lower CI	Upper CI	*p*-value
All-cause mortality							
Total number included in analysis	174	183					
Number deceased within 12 months	8	8	Unadjusted HR	1.05	0.39	2.80	0.923
% deceased within 12 months	4.60	4.37	Adjusted HR[a]	0.94	0.35	2.51	0.898
COPD/respiratory-related mortality							
Total number included in analysis	174	183					
Number deceased within 12 months	2	6	Unadjusted HR	0.34	0.07	1.71	0.192
% deceased within 12 months	1.15	3.28	Adjusted HR[a]	0.33	0.07	1.66	0.179
Total number of MACEs							
Total number included in analysis	174	183					
Number with ≥ 1 MACE	1	2					
Total MACEs	1	2					
Mean MACE rate	0.01	0.01	Unadjusted IRR	0.54	0.10	2.84	0.467
SD MACE rate	0.08	0.11	Adjusted IRR[a]	NA	NA	NA	NA

a Adjusted for: centre (as a random effect), recruitment setting (primary or secondary care), age centred on the mean, sex (male/female), smoking status (current vs. ex), FEV_1% predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long-term antibiotics.

Secondary outcome: lung function (% predicted forced expiratory volume in 1 second and forced vital capacity)

Lung function data from spirometry were available for the per-protocol analysis from 256 participants at baseline (174 bisoprolol, 182 placebo), 153 participants (77 bisoprolol, 76 placebo) after 6 months of treatment, and for 44 (26 bisoprolol, 18 placebo) participants after 12 months of treatment (see *Table 27*). In the per-protocol analysis, lung function was not found to differ significantly between the treatment groups. The overall difference in FEV_1 per cent predicted (across the 12-month period) was −2.58% (−8.80, 3.64) between the adherent/compliant groups. A similar pattern was observed for per cent predicted FVC with a difference of −1.63% (−15.85, 12.59) (see *Table 27*).

Secondary outcome: Transition Dyspnoea Index

In the per-protocol population, the mean total TDI scores at 6 and 12 months for each treatment group were negative, suggesting some deterioration in the symptom of breathlessness during the treatment period; however, there were no significant differences between the treatment groups at 6 and 12 months (*Tables 28* and *29*).

Secondary outcome: chronic obstructive pulmonary disease assessment test, EuroQoL-5 Dimensions, five-level version

The CAT scores were very similar between the treatment groups at baseline (*Table 30*) and declined for both groups during the 12-month treatment period. The CAT scores did not differ significantly between the treatment groups at 6 or 12 months with a between-group difference in the CAT score at the end of the 12-month treatment period, mean (95% CI) difference −0.54 (−2.32 to 1.25), suggesting no significant difference between the groups on the impact of COPD on the participants' overall health and well-being.

EuroQoL-5 Dimensions, five-level version utility scores were balanced between the two treatment groups at baseline (*Table 31*) for the per-protocol sample, and there was very little change during the 12-month treatment period and no significant differences between the two treatment groups. The EQ-5D-5L VAS scores of the participants allocated to bisoprolol and placebo were balanced at baseline, and the VAS scores of the two treatment groups did not differ significantly throughout the 12-month treatment period.

TABLE 27 Lung function (per-protocol analysis)

Outcome	Time point		Bisoprolol	Placebo		Overall mean difference	Lower CI	Upper CI	*p*-value
% Predicted FEV_1	Baseline	*N*	174	182					
		Mean	49.41	51.21					
		SD	17.79	18.19					
	6 months	*N*	77	76					
		Mean	49.04	49.44	Unadjusted	−0.43	−6.18	5.32	0.882
		SD	18.54	18.64	Adjusted[a]	−0.10	−2.97	2.77	0.944
	12 months	Total *N*	26	18					
		Mean	45.54	54.31	Unadjusted	−8.78	−19.61	2.05	0.120
		SD	20.00	14.62	Adjusted[a]	−2.58	−8.80	3.64	0.424
% Predicted FVC	Baseline	*N*	173	180					
		Mean	97.77	84.62					
		SD	198.30	22.07					
	6 months	*N*	71	67					
		Mean	83.85	81.63	Unadjusted	2.62	−5.53	10.78	0.530
		SD	29.79	24.32	Adjusted[a]	1.73	−4.86	8.32	0.608
	12 months	*N*	25	17					
		Mean	84.71	88.94	Unadjusted	−4.22	−18.24	9.79	0.558
		SD	26.46	15.59	Adjusted[a]	−1.63	−15.85	12.59	0.824

CI, confidence interval; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; SD, standard deviation.
a Adjusted for: centre (as a random effect), recruiting site (primary or secondary care), age centred on the mean, gender (male/female), smoking in pack years, FEV_1% predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long-term antibiotics.

TABLE 28 Change in breathlessness as quantified by TDIs – total score (per-protocol analysis)

Outcome	Time point		Bisoprolol	Placebo	Mean difference[a]		Lower CI	Upper CI	*p*-value
Total score	6 months (TDI score)	*N*	153	161					
		Mean	−0.510	−0.062	Unadjusted	−0.540	−1.150	0.060	0.078
		SD	2.810	2.828	Adjusted[b]	−0.590	−1.190	0.020	0.059
	12 months (TDI score)	*N*	143	151					
		Mean	−1.406	−0.868	Unadjusted	−0.610	−1.390	0.170	0.126
		SD	3.733	3.352	Adjusted[b]	−0.490	−1.280	0.290	0.219

a Mean difference represents overall mean difference between bisoprolol and placebo.
b Adjusted for: centre (as a random effect), recruitment setting (primary or secondary care), age centred on the mean, sex (male/female), smoking status (current vs. ex), FEV_1% predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long-term antibiotics, baseline BDI.

Summary

In summary, the BICS trial was adversely affected by the COVID-19 pandemic with recruitment being closed after 515 of the target 1574 participants had been recruited and randomised. Overall, there was no evidence that bisoprolol significantly reduced the number of COPD exacerbations requiring treatment compared to placebo. There was some

TABLE 29 Change in breathlessness as quantified by TDIs – individual domains (per-protocol analysis)

Outcome	Time point		Bisoprolol	Placebo		Mean difference[a]	Lower CI	Upper CI	*p*-value
Change in functional impairment	6 months (TDI score)	*N*	155	161					
		Mean	−0.123	0.025	Unadjusted	−0.170	−0.390	0.050	0.127
		SD	1.059	0.968	Adjusted[b]	−0.200	−0.420	0.030	0.084
	12 months (TDI score)	*N*	143	152					
		Mean	−0.378	−0.237	Unadjusted	−0.150	−0.420	0.120	0.269
		SD	1.304	1.144	Adjusted[b]	−0.120	−0.400	0.150	0.372
Change in magnitude of task	6 months (TDI score)	*N*	155	164					
		Mean	−0.168	0.030	Unadjusted	−0.210	−0.430	0.000	0.055
		SD	0.979	1.024	Adjusted[b]	−0.220	−0.440	−0.010	0.046
	12 months (TDI score)	*N*	144	153					
		Mean	−0.451	−0.235	Unadjusted	−0.240	−0.510	0.040	0.089
		SD	1.278	1.180	Adjusted[b]	−0.200	−0.480	0.080	0.157
Change in magnitude of effort	6 months (TDI score)	*N*	158	164					
		Mean	−0.222	−0.091	Unadjusted	−0.170	−0.400	0.070	0.173
		SD	1.132	1.096	Adjusted[b]	−0.180	−0.410	0.060	0.144
	12 months (TDI score)	*N*	144	154					
		Mean	−0.569	−0.403	Unadjusted	−0.200	−0.490	0.080	0.167
		SD	1.388	1.245	Adjusted[b]	−0.140	−0.430	0.150	0.341

a Mean difference represents overall mean difference between bisoprolol and placebo.
b Adjusted for: centre (as a random effect), recruitment setting (primary or secondary care), age centred on the mean, sex (male/female), smoking status (current vs. ex), FEV_1% predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long-term antibiotics, baseline BDI.

evidence that bisoprolol reduced COPD-related mortality; however, the numbers were small and bisoprolol did not reduce all-cause mortality. There was no evidence overall that bisoprolol significantly increased emergency hospital admissions (COPD related or COPD unrelated). Lung function was similar across the 12-month follow-up in the two groups, although the COVID-19 pandemic halted measurement of lung function. When compared with participants allocated to placebo, participants taking bisoprolol did not report any clinically and/or statistically significant worsening of breathlessness or COPD health and well-being. Overall, the safety profile of bisoprolol was similar to placebo. Although bisoprolol was not associated with an excess of respiratory side effects, there was an excess of some well-described side effects (cold peripheries, hypotension). There was no evidence that the treatment effect differed in any of the pre-specified subgroups or was affected by the COVID-19 pandemic.

TABLE 30 Patient-reported outcomes – CAT score (per-protocol analysis)

Outcome, time point		Bisoprolol	Placebo		Overall mean difference	Lower CI	Upper CI	*p*-value
CAT score								
Baseline	*N*	174	183					
	Mean	22.41	22.11					
	SD	7.93	8.07					
6 months	*N*	161	175					
	Mean	20.61	18.99	Unadjusted	1.78	−0.02	3.59	0.054
	SD	8.56	8.96	Adjusted[a]	1.43	−0.29	3.15	0.104
12 months	*N*	156	162					
	Mean	19.91	19.72	Unadjusted	0.55	−1.33	2.44	0.564
	SD	8.64	8.98	Adjusted[a]	−0.54	−2.32	1.25	0.558

a Adjusted for: centre (as a random effect), recruiting site (primary or secondary care), age centred on the mean, gender (male/female), smoking in pack years, FEV_1% predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long-term antibiotics.

TABLE 31 Patient-reported outcomes (per-protocol analysis)

Outcome, time point		Bisoprolol	Placebo		Mean difference[a]	Lower CI	Upper CI	*p*-value
EQ-5D-5L utility								
Baseline	*N*	172	180					
	Mean	0.60	0.59					
	SD	0.26	0.25					
6 months	*N*	159	167					
	Mean	0.60	0.63	Unadjusted	−0.03	−0.08	0.03	0.295
	SD	0.26	0.27	Adjusted[b]	−0.02	−0.07	0.04	0.525
12 months	*N*	153	159					
	Mean	0.62	0.62	Unadjusted	−0.01	−0.07	0.04	0.687
	SD	0.27	0.25	Adjusted[b]	0.01	−0.04	0.07	0.668
EQ-5D-5L VAS								
Baseline	*N*	173	181					
	Mean	61.96	61.57					
	SD	21.02	21.19					
6 months	*N*	157	167					
	Mean	60.09	63.95	Unadjusted	−4.29	−8.97	0.40	0.074
	SD	23.48	20.66	Adjusted[b]	−4.76	−9.40	−0.13	0.045
12 months	*N*	152	159					
	Mean	59.86	61.15	Unadjusted	−1.36	−6.00	3.28	0.566
	SD	21.58	20.37	Adjusted[b]	−1.23	−5.95	3.49	0.609

a Mean difference represents overall mean difference between bisoprolol and placebo.
b Adjusted for: centre (as a random effect), recruitment setting (primary or secondary care), age centred on the mean, sex (male/female), smoking status (current vs. ex), FEV_1% predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long-term antibiotics.

Chapter 5 Cost-effectiveness

Methods

Aim and objectives of economic evaluation

The aim of the economic evaluation was to estimate the cost-effectiveness of bisoprolol (plus usual care) compared to placebo (i.e. usual care only) in preventing exacerbations of COPD requiring treatment, in a population at high risk of exacerbation.

The objectives were originally to

1. assess the cost-effectiveness of bisoprolol in preventing exacerbations compared to placebo over the 12-month follow-up of the trial, and
2. assess the cost-effectiveness of bisoprolol in preventing exacerbations compared to placebo over a lifetime horizon.

As the trial was stopped (due to COVID-19 pandemic) before the target sample size was reached, the main study estimate of outcome (number of exacerbations) will be underpowered. The health economics data were analysed as planned for the 12-month cost-effectiveness analysis, with cautioning about interpreting the results due to the reduced sample size. Due to the underpowering of the main study outcome estimate, the planned lifetime cost-effectiveness analysis was not conducted. The planned analysis of health economic outcomes in relation to the phases of COVID-19 lockdown was not conducted because in the absence of a clinic effect on exacerbations, such a health economic analysis would be highly unlikely to alter the interpretation of the main study findings or have implications for clinical practice.

Overview of economic evaluation

The economic evaluation takes an NHS and Personal Social Services perspective, in line with the NICE reference case.[90]

The population and comparators considered are those described earlier in this report.

The analysis made use of data collected during the trial as follows: healthcare resource use data, quality-of-life utilities estimated from the EQ-5D-5L questionnaire and the exacerbation rate.

Table 32 illustrates the timing of economic data collection. The EQ-5D-5L questionnaire, number of exacerbations requiring treatment and inhaled medication are collected at baseline, at 6-month and 12-month follow-up. Health services resource use is collected at 6- and 12-month follow-up.

The economic evaluation follows establish guidance and will be reported in line with the Consolidated Health Economic Evaluation Reporting Standards guideline.[91] Stata 17 was used for all analyses (StataCorp. 2021; Stata Statistical Software, release 17; College Station, TX, USA).

TABLE 32 Data-collection timings

Data collected	Baseline	6 months	12 months
EQ-5D-5L	✓	✓	✓
Exacerbations[a]	✓	✓	✓
Health services resource use[b]	×	✓	✓
Medication: inhaled and other regular	✓	✓	✓

a Number of exacerbations needing treatment in previous 6 months, except at baseline when in previous 12 months.
b Resource use collected for previous 6 months.

Identification, measurement and valuation of resources

Resource use categories consist of the intervention, COPD maintenance inhaled medication, other medication, oxygen therapy, exacerbation treatment and health service use (primary care, inpatient stays, outpatient visits and emergency admissions not due to COPD).

The intervention resource use comprises bisoprolol and titration-monitoring visits (over a 7-week period). Due to restrictions applied during the national COVID-19 lockdown, titration visits moved from face to face prior to the lockdown period, to telephone calls during and after the lockdown period. To enable participants to monitor their blood pressure while at home and to provide feedback to the nurse, all participants who attended telephone titration visits were also sent a digital blood pressure monitor. The intervention resource use categories are bisoprolol (usage during titration and remaining follow-up, dosage-specific), nurse time taken for titration visits and blood pressure monitors sent to participants during and after lockdown. Nurse time for titration visits was estimated using expert opinion. Medication cost during the titration period was allocated as 168 tablets per participant, as this was the amount of tablets given to each participant. Participant's fixing dose of bisoprolol set at the end of the titration period was taken from trial data and applied for the remainder of the follow-up period.

Non-COPD maintenance medication was collected; however, due to the diverse nature of the medication, we did not attach a value and include in costs.

Exacerbations costs are spilt into two categories: (1) medication used in treating exacerbations, and (2) location of treatment of exacerbations (home, care at home to prevent hospitalisation, or hospital).

Resource use is collected using a modified version of the CSRI,[92] collecting all categories described above.

Resource use was valued by applying unit costs (Great British pounds) for the 2021–2 price year (*Table 33*). Unit cost sources include NHS reference costs for hospital costs,[93,94] the *British National Formulary* (BNF) for medication costs,[95] the Personal Social Services Research Unit (PSSRU) for primary care costs[96,97] and literature for oxygen costs.[98] Where necessary, inflation was adjusted for using the PSSRU inflation index.[97]

TABLE 33 Unit costs and sources

Resource	Unit	Unit cost (£)	Source
Intervention			
Bisoprolol	1.25 mg	0.03	BNF[95]
Titration (nurse visits prior to lockdown)	Per contact	36	PSSRU 2022[97]
Titration (nurse visits during and after lockdown)	Per contact	24	PSSRU 2022[97]
Blood pressure monitor	Per participant	21.97	Trial team
Exacerbations			
Treatment (medication – antibiotics)	Per 7-day course	2.44	BNF[95]
Treatment (medication – oral corticosteroids)	Per 7-day course	7.28	BNF[95]
Treatment (medication – inhaled)	Per day	0.53	BNF[95]
Treatment (medication – nebuliser)	Per day	1.21	BNF[95]
Treatment (medication – saline nebuliser)	Per day	1.52	BNF[95]
Treatment – oxygen	Per day	7.34	Murphy *et al.*[98]
Treatment (location – home)	Per exacerbation	50.50	PSSRU[97]

TABLE 33 Unit costs and sources (*continued*)

Resource	Unit	Unit cost (£)	Source
Treatment [location – care at home to prevent hospital admission (or facilitate earlier discharge from hospital)]	Per exacerbation	457.66	NHS ref costs[93] and PSSRU[97]
Treatment (location – hospital)	Per day	318.22	NHS ref costs[93]
COPD maintenance therapy			
Various			BNF[95]
Long-term oxygen therapy			
Long-term oxygen ventilation package	Per 6 months	2678	Murphy *et al.*[98]
Inpatient			
General medical ward	Per day	471	NHS ref costs[94]
Long-stay ward		471	NHS ref costs[94]
Urology		596	ISD
Surgery		582	ISD
Orthopaedics		512	ISD
Intensive care		2250	ISD
Hospice		206	PSSRU[97]
Outpatient			
Outpatient attendance	Per visit	165	NHS ref costs[93]
Day case	Per visit	1038	NHS ref costs[93]
A&E attendance (no overnight admission)	Per visit	242	NHS ref costs[93]
Ambulance	Per use	390	NHS ref costs[93]
Primary care			
Emergency GP visit		97	PSSRU[96]
Routine GP visit		35	PSSRU[97]
Community/district nurse		54	NHS ref costs[93]
Hospital at home team		110	NHS ref costs[93]
Other primary care		80	NHS ref costs[93]
Non-COPD emergency admissions			
Ambulance		390	NHS ref costs[93]
Non-elective bed-day		362	NHS ref costs[94]
A&E attendance		242	NHS ref costs[93]

A&E, accident and emergency; ISD, Information Services Division, NHS Scotland.

Identification, measurement and validation of outcomes

The primary economic outcome is the QALY, a combination of quality and length of life. The secondary outcome is the number of exacerbations requiring treatment.

Quality of life is measured using the self-reported questionnaire EQ-5D-5L,[99] completed at baseline, 6 and 12 months. The EQ-5D-5L is valued using recommended crosswalk mapping[100] and the UK data set. Standard area under the curve methods were used[101] to calculate QALYS, and the QALYs were adjusted for baseline utilities.[102]

The number of exacerbations were self-reported at the 6-month and 12-month follow-ups.

Analysis

The full analysis set comprises the ITT population. The within-trial analysis does not require discounting as it is 1 year in length.[90] Free text in the data was checked for spellings and sense-checked for accuracy, and any resulting major alterations were discussed with the trial team and all alterations were recorded in the Stata code.

The pattern of missing data was assessed, and found to be missing at random, multiple imputation using chained equations was applied.[103] Proportions of missing data are reported for resource use and EQ-5D-5L.

Mean, per participant complete case results (all resource use and EQ-5D-5L questionnaires are complete) are presented for resource use categories, costs, health utilities (EQ-5D-5L) and QALYs, but not compared statistically.

The differences in multiple imputed total mean costs and QALYs are analysed using general linear models.[104] These were adjusted for baseline variables that were significant predictors of costs and QALY. For costs, these were baseline medication count, baseline EQ-5D-5L, whether the participant was recruited before or during the COVID-19 lockdown period and age. For QALYs, these were the number of days follow-up in the trial, baseline EQ-5D-5L, age and gender. A cluster command was used for centre number.

Total mean costs and QALYs for each arm are presented with 95% CIs. Non-parametric bootstrapping was used to capture sampling uncertainty in the observed data.[105] The results of the bootstrapping were used to calculate 95% CI around the difference in costs and QALYs, and results are also presented on a cost-effectiveness plane and using a cost-effectiveness acceptability curve (CEAC).[106] Uncertainty in the results is assessed using threshold analysis to identify the value at which key parameters change the conclusion of the cost-effectiveness analysis.[107] The cost-effectiveness of the intervention is assessed using the current NHS threshold of £20,000–£30,000 per QALY.

The exacerbation outcome was complete and no imputation was required for missing data, and results are presented as unadjusted in line with the main trial outcome.

Assumptions

A number of pragmatic assumptions were taken in this analysis:

- Intervention costs – during the trial each participant was given a bottle of 168 × 1.5 mg bisoprolol tablets for titration purposes; the cost of bisoprolol during titration was calculated as this bottle (over 7 weeks), due to the varying nature of each participant's titration journey.
- Where the fixed dose of bisoprolol was not available, we applied an arm-specific mean.
- Patients randomised prior to March 2020 had face-to-face titration visits, and those randomised afterwards had telephone calls.
- Titration was carried out by nurse, 50 : 50 Band 5 and 6; we apply average cost of these two bands for 45 minutes for titration face to face and 30 minutes for titration remotely.

Environmental sustainability

An unexpected impact of COVID-19 on delivering the intervention was titration visits changing from face to face to remotely via telephone, and this has an impact on the environment. Changing the format of the titration visits was successful and has been implemented in a subsequent trial.[108] Patient transport accounts for 5% of NHS carbon emissions (Delivering a Net Zero National Health Service – NHS),[109] and with the NHS target of net zero by 2045, reducing patient journeys could contribute to reducing carbon emissions. Using a triple bottom line approach to assess new heath interventions is a key step in addressing the carbon footprint of NHS, evaluating effectiveness, cost and environmental sustainability; therefore, an environmental assessment is included in this report.[110,111]

To assess the impact of changing titration visits from face to face to telephone, an average distance for an outpatient appointment transport journey of 19 km[112] has been taken from literature, and this has been combined with the average number of titration visits during BICS, using a mid-range petrol car. Results are presented as CO_2.[113]

Results

A total of 514 participants are included in the ITT cohort, 259 in the bisoprolol arm and 255 in the placebo arm and 24 participants died during the trial.

Missing data

Missing data at baseline and each follow-up point are presented in *Table 34*. For resource use data, there were slightly higher missing data in the placebo arm compared to the bisoprolol arm, up to 9%. There was slightly increased proportion of missing data in the bisoprolol arm compared to placebo arm for the EQ-5D-5L questionnaire.

Complete case results

There were 378 (73.5%) participants with complete case data (full resource use and QALY data), 189 (73.0%) in the bisoprolol arm and 189 (74.1%) in the placebo arm.

Complete case resource use results (*Table 35*) show higher use of intervention, oxygen and exacerbation location treatment in bisoprolol compared to placebo. In total, 34 participants reported using long-term oxygen during the treatment period, 20 in the bisoprolol arm and 14 in placebo; hence, the higher use of oxygen in the bisoprolol arm. The resource use is higher for location of exacerbation due to the slightly higher number of reported exacerbations in the bisoprolol arm (2.1 vs. 2.0 respectively for complete case). Complete case results also show slightly increased number of primary care contacts, outpatient visits and non-COPD medication in the placebo arm compared to bisoprolol.

Complete case costs mirror the differences between arms described above for resource use: higher costs for the intervention, oxygen and exacerbations in the bisoprolol arm, and higher costs for primary care and outpatient visits in the placebo arm. Overall, complete case total costs are higher in the bisoprolol arm compared to placebo arm, £3866 and £3511 (*Table 36*).

Complete case health utilities calculated from the EQ-5D-5L questionnaire are higher in the bisoprolol arm compared to placebo at baseline, 6- and 12-month follow-ups (*Table 37*). This difference between arms is reflected in the QALY results, with 0.576 QALYs in the bisoprolol and 0.598 in the placebo arm.

TABLE 34 Missing cost and utility data

	Bisoprolol	Placebo	Total
Resource use			
6-month follow-up	11 (4.3%)	14 (5.5%)	25 (4.9%)
12-month follow-up	13 (5.0%)	20 (7.8%)	33 (6.4%)
Full follow-up	15 (5.8%)	22 (8.6%)	37 (7.2%)
EQ-5D-5L			
Baseline	3 (1.2%)	4 (1.6%)	7 (1.4%)
6-month follow-up	51 (19.7%)	47 (18.4%)	98 (19.1%)
12-month follow-up	63 (24.3%)	60 (23.5%)	123 (23.9%)
Full follow-up	76 (29.3%)	73 (28.6%)	149 (29.0%)

TABLE 35 Complete case resource use

Resource type	Bisoprolol Mean (SD) *n* = 189	Placebo Mean (SD) *n* = 189
Intervention		
Number of daily bisoprolol tablets	2.3 (1.3)	N/A
Number of titration visits	3.2 (1.1)	N/A
Non-intervention		
Inhaled medication	4.6 (1.5)	4.6 (1.5)
Oxygen	0.09 (0.29)	0.05 (0.22)
Exacerbation treatment – antibiotics	1.7 (1.8)	1.7 (1.6)
Exacerbation treatment – oral corticosteroids	1.6 (1.7)	1.6 (1.5)
Exacerbation treatment – oxygen	0.02 (0.13)	0.01 (0.07)
Exacerbation treatment – bronchodilator	0.30 (0.71)	0.40 (0.93)
Exacerbation – treatment at home	1.9 (1.9)	1.8 (1.6)
Exacerbation – treatment in community to prevent hospitalisation or facilitate earlier discharge from hospital	0.08 (0.35)	0.06 (0.34)
Exacerbation – treatment in hospital	0.26 (0.61)	0.24 (0.59)
Primary care	5.1 (5.9)	5.9 (6.3)
Inpatient stays	0.11 (0.36)	0.12 (0.44)
Outpatient visits	1.5 (2.8)	2.2 (2.8)
Emergency admissions	0.16 (0.52)	0.14 (0.48)
Non-COPD medication	4.9 (3.3)	5.8 (3.7)

TABLE 36 Complete case costs

Resource type	Bisoprolol Mean (SD) *n* = 189	Placebo Mean (SD) *n* = 189
Intervention costs	£127 (£37)	£0
Inhaled medication	£822 (£629)	£809 (£607)
Oxygen	£413 (£1388)	£227 (£1008)
Exacerbation	£827 (£1771)	£721 (£1918)
Primary care	£347 (£443)	£378 (£434)
Inpatient stays	£357 (£1747)	£320 (£1581)
Outpatient visits	£356 (£607)	£502 (£682)
Emergency stays	£619 (£2460)	£555 (£3462)
Total costs	£3866 (£4899)	£3511 (£5207)

TABLE 37 Complete case health utilities and QALYs

	Bisoprolol	Placebo
	Mean (SD)	Mean (SD)
EQ-5D-5L utilities baseline	0.587 (0.263)	0.591 (0.256)
EQ-5D-5L utilities 6-month follow-up	0.573 (0.280)	0.609 (0.271)
EQ-5D-5L utilities 12-month follow-up	0.581 (0.284)	0.588 (0.278)
Total QALYs over 12-month follow-up	0.576 (0.257)	0.598 (0.248)

TABLE 38 Cost-effectiveness results

	Bisoprolol	Placebo	
	Mean (95% CI)	Mean (95% CI)	Difference
Total costs[a]	£4058 (£3485 to £4631)	£3422 (£2869 to £3975)	£636 (−£118 to £1391)
Total QALYs[a]	0.552 (0.532 to 0.572)	0.587 (0.565 to 0.609)	−0.035 (−0.059 to −0.010)
Cost per QALY	Dominated		
Exacerbations	2.03 (1.81 to 2.25)	2.01 (1.79 to 2.24)	0.02 (−0.336 to 0.297)
Cost per exacerbation	£31,800		

a Multiple imputed and adjusted results.

Cost-effectiveness

Multiple imputed and adjusted results show higher total costs (£636, 95% CI −£118 to £1391) in the bisoprolol arm compared to placebo arm (*Table 38*). The 95% CI is wide and crosses '0', indicating that this result is uncertain.

Quality-adjusted life-years in the placebo arm are higher than in the bisoprolol arm, a difference of 0.035 (95% CI 0.059 to 0.010). These results suggest that including bisoprolol alongside usual care for COPD patients is slightly more costly and less effective than placebo and this intervention would be described as 'dominated'. Cost per exacerbation result is £31,800 per exacerbation, and this result cannot be compared to the NICE willingness-to-pay threshold to assess cost-effectiveness and would also be considered dominated.

However, care should be taken in interpreting these results due to the reduced sample size; the original target sample size was 1574; however, due to the COVID-19 pandemic, the final sample size was 515 (with 514 in the ITT population).

Threshold analysis

In order for bisoprolol to be considered cost-effective, the incremental cost-effectiveness ratio would need to be £20,000 or below and in favour of bisoprolol. This would require a difference in QALYs between arms and in favour of bisoprolol of 0.03.

Cost-effectiveness plane

The bootstrapped samples are plotted on the cost-effectiveness plane (*Figure 7*); this shows that most samples were more costly and less effective in the bisoprolol arm, resulting in the intervention being dominated.

Cost-effectiveness acceptability curve

The CEAC shows that at the current NICE willingness-to-pay threshold of £20,000, there is less than a 1% chance of the bisoprolol intervention being cost-effective (*Figure 8*).

Environmental sustainability considerations

The mean number of titration visits was 3.2, and each participant will reduce their carbon footprint by 22.4 kg CO_2.

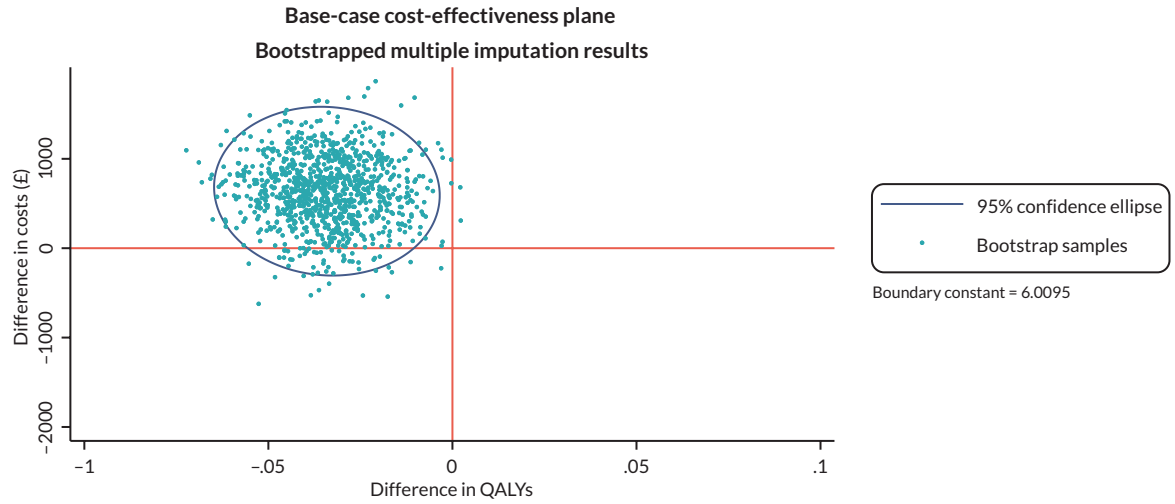

FIGURE 7 Cost-effectiveness plane (bootstrapped samples).

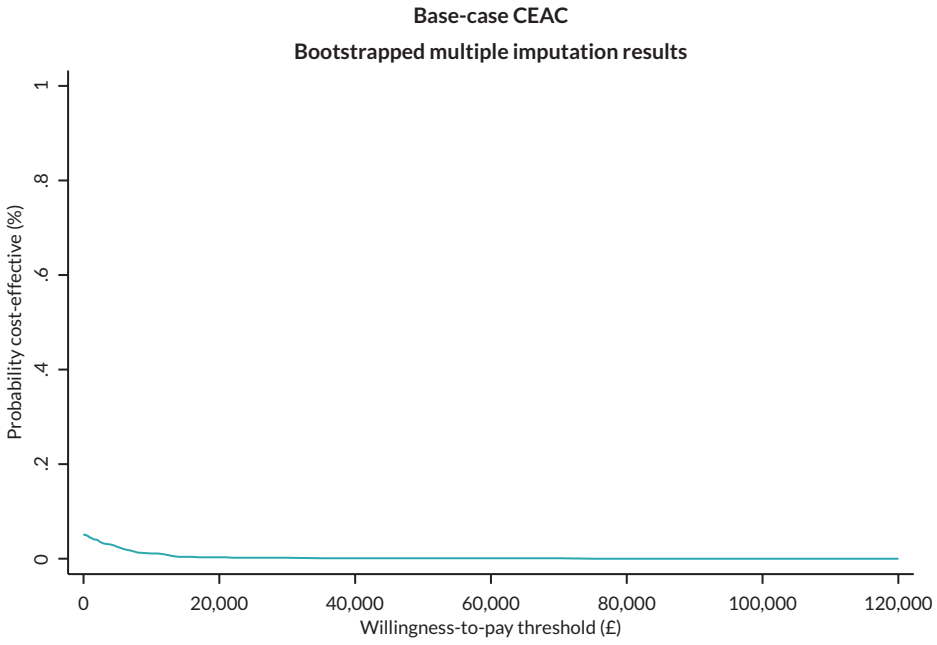

FIGURE 8 Cost-effectiveness acceptability curve.

Chapter 6 Discussion

Main results

This COVID-19-affected trial closed to recruitment after 515 participants had been enrolled when the funder indicated they could not fund the extension to the recruitment period that would have been required to meet the recruitment target of 1574. Consequently, the study was underpowered and findings should be interpreted cautiously. The results of this trial show that for people with COPD at high risk of exacerbation, the addition of the beta1-blocker bisoprolol to routine treatment confers no overall clinical or health economic benefit. This result was evident from both the ITT and the per-protocol analyses. For the primary outcome measure, bisoprolol had no effect on the total number of patient-reported exacerbations of COPD requiring changes in management during the 1-year treatment period. An important finding, with implications for clinical practice, was that bisoprolol was not associated with any clinically significant safety concerns. For 9 of the 11 pre-specified secondary outcome measures, the addition of bisoprolol had no clinical benefit. Notably, the addition of bisoprolol was not associated with a clinical deterioration in COPD as quantified by the secondary outcomes of COPD exacerbations requiring hospital admission, lung function and impact of COPD on health and well-being (CAT score). For the secondary outcome of COPD-related mortality, there was some evidence that this was reduced with bisoprolol; however, the numbers were small and bisoprolol was not associated with a reduction in all-cause mortality. For the secondary outcome of breathlessness quantified by the TDI, bisoprolol was associated with a change in score, indicative of an increase in breathlessness; however, the difference was of borderline statistical significance. Overall, the safety profile of bisoprolol was similar to that of placebo, with bisoprolol not being associated with an excess of SAEs or an excess of total or respiratory ARs; however, as expected, there was an excess of some well-described side effects (cold peripheries, hypotension).

Although this trial did not recruit the required number of participants to achieve intended statistical power, the estimates of the effect size of bisoprolol were close to unity and consideration of the CIs suggests that while the ITT analysis narrowly failed to exclude a predefined clinically important ≥ 15% reduction in COPD exacerbations, the per-protocol analysis did exclude a ≥ 15% reduction in COPD exacerbations. These findings suggest that little will be gained by conducting a further trial of bisoprolol in people with COPD having COPD exacerbations as the primary outcome. Our conclusion that the addition of bisoprolol to the routine treatment of people with COPD is not clinically beneficial and cannot be recommended is supported by a published trial (see below), and we anticipate that an ongoing trial of bisoprolol in COPD (see below) along with subsequent meta-analyses of these trials will provide further support for our findings and conclusion.[87,108]

Relevance to existing literature

The current study investigated whether the beta1-blocker, bisoprolol, was of clinical benefit when added to the routine treatment of people with COPD who did not have an established cardiovascular indication but were at high risk of exacerbation. The justification for the current study was reports from secondary analyses of observational and interventional studies of beta-blockers used for cardiovascular indications, that not only was beta-blocker use safe in people with COPD, but it was also associated with reductions in exacerbations and mortality. Furthermore, this beneficial association was evident in people with COPD who did not have evidence of cardiovascular disease and appeared to be specific to beta-blockers. During the conduct of BICS, closer scrutiny of observational studies, additional observational studies and an RCT indicated that beta-blockers (specifically, metoprolol) may be detrimental for people with COPD and that any beneficial effect on COPD exacerbations is limited to people with COPD with cardiovascular disease in whom beta-blockers have proven clinical benefit.

Since BICS commenced, undoubtedly the most important development, in terms of the debate on the safety of beta-blockers in COPD and the potential of beta-blockers to reduce exacerbations of COPD was the 2019 report from the BLOCK COPD trial.[87] BLOCK COPD was a multicentre, randomised, double-blind, placebo-controlled trial of metoprolol in people with moderate/severe COPD (FEV_1/FVC < 0.7, FEV_1 < 80% predicted) conducted in the USA. Participants

were randomised 1 : 1 to extended-release metoprolol succinate or placebo with a 6-week dose-titration phase resulting in final doses of 25 mg, 50 mg or 100 mg once daily, and the total treatment period was 52 weeks. Although the inclusion criteria for BLOCK COPD were intended to recruit people with COPD at increased risk of exacerbations, they differed from the BICS inclusion criterion of ≥ 2 exacerbations in the previous year. BLOCK COPD included people with COPD with ≥ 1 exacerbation in the previous year treated with antibiotics and/or systemic corticosteroids, or a visit to an emergency department or hospitalisation for a COPD exacerbation during the previous year or had been prescribed supplemental home oxygen for at least 12 hours a day. The exclusion criteria were very similar to the BICS, apart from the presence of specified changes on an electrocardiogram (ECG) recorded at baseline in BLOCK COPD (left bundle branch block, bifascicular block, ventricular tachyarrhythmia, atrial fibrillation, atrial flutter, supraventricular tachycardia or second-/third-degree heart block). The primary outcome was the time to the first moderate/severe COPD exacerbation, and the study sample size of 1028 was powered to detect a 15% reduction in the probability of an exacerbation in the year treatment period. BLOCK COPD was terminated prematurely after the recruitment of 532 participants when a planned interim analysis indicated futility with respect to the primary outcome and raised safety concerns. There were no significant between-group differences in the median time to first exacerbation (202 days metoprolol, 222 days placebo group) (HR metoprolol vs. placebo 1.05, 95% CI 0.84 to 1.32, $p = 0.66$). Similarly, there was no difference in the rate of COPD exacerbations between the metoprolol and placebo groups; rate ratio 1.05, 95% CI 0.85 to 1.28. The safety concern was that metoprolol use was associated with a higher risk of COPD exacerbation leading to hospitalisation, specifically an increase in severe (HR 1.91, 95% CI 1.29 to 2.83) and very severe exacerbations (HR 2.08, 95% CI 1.37 to 3.14). Metoprolol use was also associated with an increased impact of COPD on health and well-being as quantified by the CAT score (difference of 1.47 points, 95% CI 0.32 to 2.62), and increased shortness of breath as quantified by the San Diego Shortness of Breath Questionnaire (difference of 4.80 points, 95% CI 1.52 to 8.07). Although metoprolol was not associated with a significant increase in mortality HR 2.13 (0.69, 6.42), the majority of deaths in the metoprolol group were attributed to COPD [7 (2.6%) vs. 1 (0.4%)]. Metoprolol was not associated with any effect on FEV_1 or the 6-minute walk distance. While the BLOCK COPD trial clearly demonstrates that participants allocated to metoprolol were more likely to experience exacerbations leading to hospitalisation, it is also evident that in the year prior to randomisation, the participants allocated to metoprolol were more likely to have had a COPD exacerbation leading to emergency department visit or hospitalisation (62.7% vs. 50.4%, $p = 0.004$). Given that the strongest predictor of future exacerbations is the history of previous exacerbations,[29] it is possible that the increased rate of exacerbations leading to hospital admissions associated with metoprolol is a consequence of the participants allocated to metoprolol being inherently more likely to be hospitalised. However, the increase in respiratory symptoms (breathlessness) and increased impact of COPD (CAT score) associated with metoprolol are more in keeping with the negative effect of metoprolol. The BLOCK COPD investigators informed us of their findings prior to the publication of their data because of their safety concerns. The BICS DMC reviewed the BLOCK COPD data in confidence and examined the BICS safety data and were content to allow BICS to continue.

The original analysis of lung function data in BLOCK COPD reported that when expressed as per cent predicted, there were no significant differences in FEV_1 over the 52-week treatment period between metoprolol and placebo.[87] However, a subsequent more detailed analysis of lung function data raised further potential safety concerns.[114] This analysis reported that when compared with placebo, over the first 28 days of treatment, metoprolol was associated with small reductions in geometric mean FEV_1 (25 ml) and arithmetic mean FVC (80 ml); however, by the end of the 52-week treatment period, although the reductions were consistently greater in the metoprolol group, they were no longer statistically significant, suggesting perhaps that some beta-blocker-induced impairment of lung function had persisted. The changes in lung function did not predict exacerbations. An accompanying editorial concluded with a note of caution, stating that because clinicians have less data to guide them, it is difficult to predict the balance of risks and benefits for patients with COPD and a cardiac indication for beta-blocker treatment.[115]

The BLOCK COPD findings appear to have influenced several subsequent systematic reviews of beta-blocker use in people with COPD, with a significant degree of caution being evident that was not present prior to BLOCK COPD. In 2021, a systematic review identified 23 observational studies and 14 RCTs investigating the effect of beta-blockers in COPD.[116] The RCTs predominantly investigated the effects of beta-blockers on FEV_1, exercise capacity and quality of life. In a meta-analysis of 5 observational studies with a total of 27,717 participants followed up for 0.76–7.2 years, beta-blockers were associated with reduced exacerbations, HR 0.78 (95% CI 0.74 to 0.82).[116] In RCTs, the only beta-blocker associated with a deterioration in lung function (FEV_1) was propranolol, with none of the individual

cardioselective beta-blockers included in the meta-analysis (atenolol, bisoprolol, celiprolol, metoprolol) being associated with significant effects on lung function in patients with COPD, regardless of baseline FEV_1 or follow-up time. This study concluded that the effects of beta-blockers in COPD remained generally positive with reduced rates of exacerbation, while propranolol was the only beta-blocker associated with a deterioration of lung function in RCTs.[116] A more recent systematic review published in 2023 investigated the safety of beta-blockers in people with COPD.[117] In total, 28 observational studies were identified, in which the indications for beta-blockers were ischaemic heart disease, heart failure and hypertension, 60,983 patients received beta-blockers and 123,579 patients were in the control groups. In 24 observational studies, 17 reported that beta-blockers were associated with reduced all-cause mortality (HR 0.38–0.91), 5 reported no change in mortality, whereas 2 high-quality studies (1 of which was BLOCK COPD) reported an increase in mortality (HR 1.19–1.37). In 15 observational studies, 7 reported a reduction in COPD exacerbations (OR/RR 0.26–0.74), 8 reported no effect on exacerbations and none reported an increase in exacerbations. The review included the findings of the BLOCK COPD trial and concluded that the data on the safety of beta-blockers in people with COPD are conflicting, with higher-quality evidence showing possible harm with their use. This review also noted that current knowledge does not allow us to answer the important question as to whether beta-blocker use in people with COPD with cardiac disease is safe. Nevertheless, the authors recommended that beta-blockers should be prescribed with caution in COPD, including patients with cardiac indication for beta-blockers. It should be noted that both of these systematic reviews included the study of Hawkins *et al.* (2009), a small (n = 27) randomised placebo-controlled trial of bisoprolol in patients with COPD and heart failure, this study is not pertinent to BICS because we excluded patients with concomitant COPD and heart failure.[118]

In 2021, the Rotterdam cohort study reported that in people with COPD with a cardiovascular indication for beta-blocker use (hypertension, coronary heart disease, atrial fibrillation, heart failure), cardioselective beta-blockers were associated with a reduced risk of COPD exacerbations (HR 0.69, 95% CI 0.57 to 0.85), whereas in people with COPD without a cardiovascular indication for beta-blocker, use of cardioselective beta-blockers were not associated with an altered risk of COPD exacerbations (HR 0.94, 95% CI 0.55 to 1.62).[119] More recently, a retrospective cohort study of patients with ACOS reported that use of cardioselective beta-blocker (HR, 0.29, 95% CI 0.11 to 0.72), angiotensin receptor blockers (HR, 0.64, 95% CI 0.44 to 0.93) and calcium channel blockers (HR, 0.66, 95% CI 0.45 to 0.97) was associated with reductions in the likelihood of COPD exacerbations of COPD suggesting that, in contrast to previous studies, any protective effect of beta-blockers on COPD exacerbations is not class specific.[44,120]

Both BICS and BLOCK COPD investigated the effect on COPD exacerbation of adding a beta-blocker to the routine treatment of people with COPD at risk of exacerbation. Both studies closed to recruitment after recruiting and randomising similar numbers of participants (BICS n = 515, BLOCK COPD n = 532). Both studies report that the addition of a beta-blocker is not associated with a clinically beneficial effect on the frequency of exacerbations or time to first exacerbation. The major difference between BICS and BLOCK COPD is that BLOCK COPD (but not BICS) raised safety concerns that could not be ignored and contributed to the early termination of recruitment. The safety concerns raised by BLOCK COPD were that the addition of metoprolol was associated with a significant increase in COPD exacerbations that resulted in hospitalisation, a significant increase in breathlessness symptoms, a significant increase in the impact of COPD on health and well-being, and a non-significant excess of deaths in those allocated to metoprolol (11 vs. 5). In contrast, in BICS, the addition of bisoprolol was not associated with an increase in COPD exacerbations resulting in hospitalisation, no significant change in the impact of COPD on health and well-being, and no significant increase in SAEs or significant increase in total or respiratory adverse events. Moreover, in BICS, bisoprolol was associated with a significant reduction in COPD/respiratory mortality, although the numbers were small and there was no difference in overall mortality between bisoprolol and placebo groups. Although in BICS, bisoprolol was associated with an increase in TDI breathlessness score, this was of borderline statistical significance.

A number of factors are likely to have contributed to the difference in the safety profiles of BICS (bisoprolol) and BLOCK COPD (metoprolol). Although BICS and BLOCK COPD recruited people with moderate/severe COPD, the sample populations differed. When compared with BLOCK COPD, the BICS sample population was at substantially higher risk of COPD exacerbation (BICS mean ~2.0 exacerbations/year, median time to first exacerbation ~90 days, BLOCK COPD ~1.2 exacerbations/year, median time first exacerbation ~200 days), whereas the BLOCK COPD sample population had more severe airflow obstruction (BICS mean FEV_1 50% predicted, 5% on long-term oxygen, BLOCK COPD mean FEV_1 40% predicted, 40% on long-term oxygen). The BICS sample population had a higher rate of using

inhaled LAMA therapies when compared with BLOCK COPD (BICS 90%, BLOCK COPD 73%), and this is a potentially important difference because LAMAs have been reported to be particularly effective in mitigating bronchoconstriction induced by beta-blockers in people with COPD or asthma.[121,122] Perhaps, the most significant contributory factor to the disparities in outcomes between BLOCK COPD and BICS was differences in the pharmacological properties of the beta-blocker interventions, with the metoprolol used in BLOCK COPD having reduced beta1 to beta2 selectivity (2.6–6.0) when compared with bisoprolol (13.5–19.6).[50,51] One could speculate that in contrast to the bisoprolol used in BICS, the increased beta2-blockade associated with metoprolol, combined with the more severe airflow obstruction and less frequent use of LAMAs in the BLOCK COPD sample population, might have led to diminished response to inhaled beta2-agonists and that metoprolol reduced or slowed response to beta2-agonists during exacerbations resulting in the need to escalate treatment to a higher level, and in doing so fulfils the definition of severe/very severe exacerbation. Similar considerations could also account for the increased breathlessness and impact on health and well-being scores reported in BLOCK COPD but not BICS.

Although BICS and BLOCK COPD have both demonstrated that beta-blockers do not reduce the likelihood of COPD exacerbation, BLOCK COPD reported clinically significant safety concerns around the use of metoprolol in people with COPD, whereas BICS indicated that the use of bisoprolol in people with COPD is not associated with the safety issues reported for metoprolol. That bisoprolol is safe to use in people with moderate/severe COPD at high risk of exacerbation is a clinically important finding with implications for everyday clinical practice for the management of people with COPD. It is well-recognised that people with COPD have a two- to threefold increased cardiovascular morbidity and mortality attributable to increased prevalence of ischemic heart disease, heart failure, arterial hypertension and arrhythmias.[12,14,20,21,123] It is well-established that beta-blockers reduce morbidity and mortality in people with ischaemic heart disease and heart failure, with beta-blocker use being a guideline recommendation for people who have suffered a myocardial infarction or have heart failure with reduced ejection fraction.[40,41,61] Despite guideline recommendations that beta-blockers should be used in people with COPD and cardiovascular conditions such as heart failure, it is well-described that many clinicians are reluctant to prescribe beta-blockers for people with COPD and cardiovascular disease;[45,52–56] consequently, many people with COPD fail to receive optimal guideline-recommended treatment for their cardiovascular disease, with consequences for morbidity, mortality and the NHS. The safety concerns reported by BLOCK COPD have heightened concerns and are likely to lead to further reductions in the use of beta-blockers in people with COPD and cardiovascular disease. The importance of BICS is that clinicians can now be confident that they can prescribe bisoprolol to people with COPD and cardiovascular disease, enabling people with COPD to receive guideline-recommended treatment for their cardiovascular disease.

Ongoing studies

At the time of writing, we are aware of several ongoing trials investigating the clinical benefit of beta-blockers in people with COPD. The Beta-blockeRs tO patieNts with CHronic Obstructive puLmonary diseasE (BRONCHIOLE) study is an open-label, randomised trial of metoprolol in patients with COPD and is ongoing in Sweden (NCT03566667).[124] The recruitment target is 1700 patients with COPD (FEV_1/FVC< 0.7), with those allocated to metoprolol starting at 50 mg a day with the aim of achieving a target dose of 100 mg; there is no placebo control, and treatment is for 52 weeks. Outcome data are being collected by clinical follow-up conducted by telephone at 6 and 12 months and accessing the Swedish National Patient Register and the Swedish Cause of Death Register. The primary outcome is a composite measure of all-cause mortality, COPD exacerbations, and cardiovascular events after 52 weeks.

Recruitment has started in the study of bisoprolol in Preventing Adverse Cardiac Events (PACE) in COPD in approximately 26 sites in Australia, New Zealand, India, Sri Lanka and other countries as required (NCT03917914).[108] In a double-blind, placebo-controlled design, 1164 patients with moderate COPD are being randomised to placebo or bisoprolol, the treatment period being 24 months. Bisoprolol is started at 1.25 mg a day and titrated to final doses of 1.25, 2.5 or 5 mg daily. The primary outcomes include all-cause mortality, hospitalisation for COPD exacerbation, hospitalisation for primary cardiac cause, and MACEs. We are aware that this study is having difficulty recruiting. PACE differs from BICS in that participants have had at least one exacerbation in the previous 24 months, treatment is for 24 months, and ECGs are recorded at baseline and throughout the treatment period (1, 3, 12 and 24 months). We have been informed by the PACE investigators that they have had similar difficulties in recruitment that BICS experienced and that they are unlike to achieve their recruitment target.

At the time of writing, the intention of the BICS, BLOCK COPD and PACE teams is that the data from the three trials will be subject to meta-analysis when the PACE data become available. The proposed analysis will address the issue of beta-blockers and exacerbations of COPD and the safety of beta-blocker use in people with COPD, of particular interest will be a comparison of safety data for metoprolol and bisoprolol.

Cost-effectiveness

Multiple imputed and adjusted cost per QALY results indicate that bisoprolol would be considered dominated, the cost per exacerbation result confirms this. However, due to the small sample size of the study, the cost-effectiveness results are underpowered, and therefore there is uncertainty in these results. Moving from face-to-face visits pre-COVID-19 pandemic to telephone consultations during and after the pandemic resulted in a decrease in participant carbon emissions.

Impact of COVID-19

Recruitment to BICS was adversely affected by the COVID-19 pandemic, with recruitment and all face-to-face contact with trial participants being suspended by the sponsor on 16 March 2020. In response to this, the outstanding titration visits, and 6- and 12-month follow-up assessments were subsequently all conducted by telephone/video call. Although we were able to collect 6- and 12-month primary outcome data effectively on all the participants randomised by 16 March 2020, the telephone/video nature of the assessment resulted in no lung function (FEV_1), heart rate or blood pressure data being captured during these encounters. Recruitment to BICS remained suspended until July 2021 when the sponsor and funder gave permission to restart recruitment in order to ascertain whether the study remained viable, and recruitment to the trial was re-established in August 2021. Discussions with PPI representatives and patients in June 2021 indicated that their confidence in attending suitably COVID-19-secure healthcare facilities was increasing because they had witnessed the effectiveness of mass COVID-19 vaccination in reducing infection rates, hospital admissions and mortality (600/month).[125] Unfortunately, recruitment proved particularly difficult after restarting in August 2021 because it coincided with the emergence of the omicron variant and well-publicised increases in infection rates, hospital admissions and mortality (6000/month).[120] The anticipated increase in recruitment capacity failed to materialise because roll-out of recruitment sites was severely affected by the resurgence in COVID-19, with clinical and research staff continuing with their COVID-19 duties, for example, patient care, COVID-19 research, mass COVID-19 vaccination. It was also noticeable that people with COPD were reluctant to take part in research ('what's in it for me') and extremely averse to any risk to their health at all ('the bisoprolol can have side effects, why would I take something that could make me ill'), one could speculate that this was a consequence of people with COPD repeatedly being told that they were 'vulnerable' and to avoid all risks. In April 2022, the funder indicated they could not fund the extension to the recruitment period that would have been required to meet recruitment targets and recruitment to the study ceased on 31 May 2022.

During the COVID-19 lockdown, advantage was taken of the changes needed to mitigate COVID-19 risk to improve the acceptability of BICS to potential participants, and these changes were approved by the TSC, DMC, REC and MHRA. In response to the need to comply with COVID-19 national IPC measures, the vulnerability of BICS participants (most/all had been shielding since March 2020) and the reluctance of people with COPD to attend healthcare facilities (consensus clinical experience), the study schedule was modified to reduce the number of face-to-face assessments to zero or a maximum of one depending on the preference of potential participants and research staff. Face-to-face visits were eliminated by the option of conducting recruitment and consent by telephone/video with PIL and consent documentation being sent by post and discussed/completed during the telephone/video encounter. If recruitment and consent were conducted face to face, all COVID-19 measures (social distancing, PPE) were implemented and if not conducted in the participant's home, the study paid for taxi travel to/from the visit if the participant did not have their own transport. As all of the subsequent titration and follow-up 'visits' were conducted remotely by telephone/video call, spirometry was not considered a viable option, principally because participant technique was likely to be suboptimal and the need to calibrate the equipment using prohibitively expensive calibration syringes before use. Moreover, not performing spirometry avoided the risks and IPC issues related to performing spirometry during the COVID-19 pandemic.[126]

Spirometry at recruitment was replaced by historical evidence of spirometry with $FEV_1/FVC < 0.7$ and $FEV_1 < 80\%$ predicted. Spirometry during dose titration was replaced by asking the participant whether their breathing has deteriorated since starting/increasing study medication, and these changes were incorporated into the online advisory algorithm. The measurement of pulse and blood pressure during the telephone/video dose-titration assessments was achieved by providing participants with a digital sphygmomanometer (Omron M2, Omron Healthcare UK Ltd, Milton Keynes, UK), which they were instructed how to use during the recruitment 'visit'. A benefit of reducing face-to-face visits to a maximum of one was that dose titrations and follow-up 'visits' could be conducted by research nurses out with the participants' geographical area, and this was particularly helpful in areas where clinical and research staff had been diverted to COVID-19 duties; for example, patient care, COVID-19 research and mass COVID-19 vaccination. The supply chain for study medication was not disrupted, supplies of medication continued to be organised by trial office staff working from home, dispensed from a central clinical trials pharmacy and couriered to participants' homes – proof of delivery signatures was not sought by couriers, so the trial office staff contacted participants to confirm delivery.

During the COVID-19 pandemic, anecdotal reports and subsequent evidence demonstrated that the incidence of exacerbations experienced by people with COPD declined by as much as 50%.[62,63] Analysis of the BICS exacerbation data comparing those recruited prior to, and after August 2021 when the shielding advice was revoked, indicated that the rate of exacerbation in those recruited after shielding advice had been revoked was 30% less than that pre-COVID-19 or during shielding. These analyses also demonstrated that the COVID-19 pandemic and associated interventions did not appreciably influence the study findings.

Strengths and limitations

The main strength of BICS was that it was a pragmatic, predominantly community-based, double-blind, randomised, placebo-controlled, UK multicentre clinical trial with a high follow-up rate for the primary clinical outcome. A total of 519 individuals were recruited in 76 of 117 UK sites that were opened up for the study, and 60% of participants were identified in primary care making it highly likely that BICS participants reflected normal clinical practice across both primary and secondary care in the UK. The 1-year treatment period allowed capture of the seasonality of exacerbations.[127]

A further strength of BICS was that it recruited a sample of people with COPD at high risk of exacerbation, the mean (SD) self-reported number of exacerbations in the 12 months prior to recruitment was 3.55 (1.95) and the mean (SD) number of exacerbations in the 12-month treatment period was 2.02 (1.83). A similar disparity between the number of exacerbations reported by participants in the year prior to the study and during the 12-month treatment period was observed in TWICS.[59] The most likely explanation for this difference is that participants were not asked for dates for the reported exacerbations in the year prior to the study, whereas during the study we asked for dates and the conventional minimum of 2 weeks between consecutive exacerbation episodes was necessary to consider exacerbations as separate.[68] This resulted in participant-reported exacerbations separated by < 2 weeks being merged. Although further factors contributing to the disparity in exacerbations before and during the study include the reduction in exacerbations during the COVID-19 pandemic and may include an over-reporting bias by participants and regression to the mean, the exacerbation frequency during the treatment period was consistent with that predicted by ECLIPSE and reported by TWICS.[29,59,62,63]

Primary outcome data (number of COPD exacerbations) were collected for 514 (99.8%) of the 515 participants who commenced the 1-year treatment period and were included in the ITT analysis. Several factors contributed to the high follow-up rate. Although, prior to March 2020, dose titration required face-to-face assessments, once titrated if participants were unable to attend for assessment, they were visited at home, contacted by telephone, or sent the questionnaires to complete at home. With the advent of COVID-19, all dose-titration and follow-up assessments were conducted remotely by telephone and/or video link. Participation and remote follow-up were further facilitated by delivering the study drug to the participants' homes using a courier. All participants who ceased taking the study drug were invited to remain in the study for follow-up, either by face-to-face assessment, telephone assessment or postal questionnaire. For participants who could not be followed up directly, for example, who failed to attend follow-up, various methods of follow-up independent of participant involvement were used. These included remote access of

electronic patient records by the participant's research team, contacting the participant's practice by e-mail/telephone/questionnaire to enquire about exacerbations (number, dates, how and where treated), and the minimum data requested were the number of exacerbations in the treatment period. The combination of follow-up methods enabled the ITT analysis to include 504 years of participant follow-up data. Inevitably, there were some participants who did not provide a full 12 months of follow-up data, for example, deaths, or for whom 12 months of follow-up data were not available even using remote follow-up method. A strength of BICS was that the statistical analytical methods used enabled the inclusion of these participants up to the point at which they were lost to follow-up, with their time in the study utilised in the offset variable during analysis.

As with all studies, there are limitations associated with BICS, the most obvious and important of which was that BICS was underpowered to detect the 15% reduction in exacerbations that it set out to demonstrate, and the results need to be interpreted with caution. The target sample size of 1574 was not achieved as recruitment was closed in May 2022 after 515 participants had been recruited because the funder considered the study to be unviable in the difficult clinical research environment present in 2022 and declined to fund the extension to recruitment needed to meet the original recruitment target. The failure to achieve our recruitment target restricted our cost-effectiveness analysis because there were insufficient data to permit the lifetime modelling of health economic data. BICS originally aimed to recruit 1574 participants, the sample size being primarily based on the findings of the observational ECLIPSE cohort study.[29] ECLIPSE reported that the best predictor of an exacerbation in a year was a treated exacerbation in the previous year. Moreover, ECLIPSE identified a frequent exacerbator phenotype defined as ≥ 2 exacerbations in the previous year, which was relatively stable for 3 years and could be reliably identified by patient report. For the frequent exacerbating patients recruited into BICS, data from ECLIPSE predicted a mean (SD) of 2.22 (1.86) exacerbations in the year of treatment, and this was supported by the findings of the TWICS study that reported a mean (SD) of 2.23 (1.97) exacerbations in a year for participants with ≥ 2 exacerbations in the previous year.[59] For BICS, the overall mean (SD) of 2.02 (1.83) exacerbations in the year of treatment is about 10% lower than the exacerbation rates reported by ECLIPSE and TWICS. Subgroup analysis of randomisation in relation to shielding advice for COVID-19 indicated that the mean exacerbation rate for participants recruited after the lifting of shielding was about 30% lower than the exacerbation rates of participants recruited prior to shielding [mean (SD) 2.12 (1.88)] which was within 5% of the exacerbation rates reported by ECLIPSE and TWICS for this patient group.[29,59]

At the onset of BICS, we were quietly confident that we could recruit 1574 participants into BICS because our experience of TWICS was that, after an initial 12-month period of below-target recruitment, 1567 people with COPD with ≥ 2 exacerbations in the previous year were recruited in 31 months, exceeding the recruitment target of 1424. Key to the success of TWICS was a rapid increase in the number of sites recruiting into the study, consequently for BICS, the intention was to rapidly open up a large number (> 100) of recruitment sites. Based on our experiences with TWICS, the recruitment target and clinical opinion that BICS would be somewhat harder to recruit to than TWICS, the original recruitment projection was to recruit 1574 participants into BICS over 36 months (August 2018–July 2021). BICS started recruitment in October 2018 and despite opening up a total of 117 sites (81 primary and 36 secondary care), by March 2020 it was apparent that recruitment was proving more difficult than anticipated with 429 (57% of the March 2020 recruitment target) participants recruited. In many respects, BICS was very similar in design to TWICS; however, several differences appear to have adversely impacted recruitment to BICS. In contrast to TWICS (three assessments in 12 months), the BICS schedule not only included these three assessments in 12 months but also included an additional four relatively closely spaced clinic visits to ensure the safe dose up-titration of the study medication as recommended in heart failure guidelines. These extra four visits proved to be a much greater burden for people with COPD than anticipated. A further unanticipated issue was the difficulties of accommodating these titration visits for participants and research staff around the time of Christmas, Easter and school holidays. Also surprisingly unpopular was the prospect of taking an extra four tablets a day (for TWICS, the maximum dose was two tablets a day). While it would have been possible for participants to have been titrated and maintained with single tablets of different strength (1.25 mg, 2.5 mg, 3.75 mg, 5 mg), the risks, logistics, complexity and manufacturing costs associated with four individual tablet strengths were considered prohibitive and a single tablet strength (1.25 mg) model was chosen. Of particular concern of using different tablet strengths was participants having almost identical bottles of different strength bisoprolol tablets around the house, increasing the risk of under and overdosing. Whereas TWICS was a trial investigating a well-established and familiar drug (theophylline) widely used to treat people with COPD, BICS investigated a drug not routinely used to treat people with COPD; moreover, it is well-described that many clinicians are

reluctant to prescribe beta-blockers for people with COPD.[45,52–56] There was evidence of some resistance to the use of beta-blockers in people with COPD when GPs were reviewing lists of potentially eligible patients. Many sites reported that recruitment to BICS was competing against recruitment to commercial trials and that there was patient fatigue with taking part in/asked to take part in many trials because people at high risk of COPD exacerbation are the focus of much academic and commercial research activity.

A limitation of BICS was that 28% of participants either did not initiate treatment with the study drug (1.6%) or ceased taking the study drug during the treatment period (26.4%). As expected, the proportion ceasing study drug was slightly higher in those allocated to bisoprolol (28.2% bisoprolol, 24.6% placebo), because of an excess of the well-recognised beta-blocker side effects of bradycardia, hypotension and cold peripheries. Although the most common reason for ceasing study medication was for respiratory reasons, this reason was not more frequent in those allocated to bisoprolol (4.6% bisoprolol, 6.3% placebo). Of those who ceased study medication, the majority (59%) did so during dose titration, and the proportion of those ceasing study medication during dose titration was similar between those allocated to bisoprolol (16.2%) and placebo (14.8%). It is remarkable that 14.8% of those allocated to placebo were unable to tolerate placebo based on an algorithm that factored in beta-blocker-associated side effects (in intolerable symptoms, blood pressure, heart rate and lung function). The proportion of participants ceasing study medication during BICS (28%) is consistent with the 26% of participants who ceased study medication during our trial of low-dose theophylline (TWICS) in people with COPD, with almost identical inclusion/exclusion criteria and very similar baseline characteristics.[59] Although consistent with TWICS, the proportion of participants ceasing study medication during BICS (28%) is much higher than the 8.7% of participants who ceased study medication during BLOCK COPD (11.2% metoprolol, 6.1% placebo); moreover, as in BICS, the most common reason for ceasing was respiratory symptoms, but in contrast to BICS, this was more frequent in those allocated to metoprolol (3.0% metoprolol, 1.1% placebo).[29,59] It is open to speculation why people with COPD in the UK were far more likely to cease study medication than people with COPD in the USA. Given the final conclusions of BLOCK COPD, it is unlikely that metoprolol was better tolerated than bisoprolol: our experience with TWICS suggests that, perhaps, people with COPD in the UK participating in trials of this type have a lower threshold for ceasing study medication. The dose-titration algorithm used in BICS was a conservative interpretation of the 'start low, go slow' advice provided in the SmPC for bisoprolol and Heart Failure Guidelines designed for use by appropriately trained nurses in primary care settings.[41,64–66] A possible consequence of the algorithm is that participants susceptible to beta-blocker side effects were titrated to zero tablets, whereas in BLOCK COPD, they remained in the trial and contributed to the reported excess of safety outcomes.

As discussed earlier, the IPC measures implemented during the COVID-19 pandemic made it impractical to measure spirometry and severely limited our ability to comment on any potential effects of bisoprolol on lung function. Although bisoprolol was not associated with a statistically significant reduction in FEV_1 at 12 months, the mean (95% CI) difference of −4.53% (−10.22 to 1.16) could be of clinical relevance. An additional analysis of the baseline lung function data of the 51 participants for whom 12-month lung function data were available allayed clinical concerns, because the difference in FEV_1 between bisoprolol and placebo groups present at 12 months was largely present at baseline.

A possible limitation of BICS relying on participant-reported exacerbations is the accuracy of such a report over a 6-month period. To facilitate recall, participants were given a diary card to make notes on exacerbations, treatment and healthcare usage. We are confident that participant recall of exacerbations is clinically relevant because patient reports are what clinicians rely on in everyday practice; furthermore, during the TWICS study, a validation exercise indicated 80% agreement between participant and GP report.[60] One of the advantages of patient-reported exacerbation data is that GP records may not be as accurate as they once were because nowadays many patients with COPD have rescue packs at home and can access help for their exacerbations through many non-GP sources; for example, pharmacies, emergency, walk-in centres, and accident and emergency departments.

The definition of an exacerbation used for BICS was that recommended by the ATS/ERS.[68] The minimum management change was treatment with antibiotics or oral corticosteroids, and consequently, the BICS only quantified moderate and severe exacerbations. However, these are the exacerbations that are the most burdensome to patients and healthcare services. A limitation of BICS is that we underestimated the frequency of symptom-defined mild exacerbations that are short-lived and treated by the patient with a temporary increase in bronchodilator therapy.[128] The identification of such mild exacerbations would have required participants to complete daily symptom diary cards which are not part of

routine clinical practice in the UK and would have added to the intrusiveness of the study. Although BICS is unable to exclude an (unlikely) effect of bisoprolol on the frequency of mild exacerbations, there were no significant differences between treatment and placebo in quality of life/impact on health status as quantified by EQ-5D-5L/CAT, suggesting either that bisoprolol had no effect on mild exacerbations or if there was an effect it did not impact on health status/healthcare usage.

Generalisability

This study has good external validity as it was of a pragmatic design that reflected normal clinical practice across both primary and secondary care in the UK. Participants remained on their existing COPD medications, and they were managed in the normal way by their usual healthcare teams and 60% of the participants were identified in primary care. The trial recruited from 76 of 117 sites that were opened (45 primary care, 31 secondary care) and that spanned the UK, many of the secondary care sites being District General Hospitals. The initiation of bisoprolol replicated its use in a typical UK primary care setting where beta-blockers are routinely commenced without an ECG being recorded (in contrast to BLOCK COPD and PACE trials), and the dose-titration schedule was a conservative interpretation of the 'start low, go slow' advice provided in the SmPC for bisoprolol and Heart Failure Guidelines designed for use by appropriately trained nurses in UK primary care settings.[41,64–66] We consider it to be highly likely that BICS participants and the use of bisoprolol are typical of normal clinical practice across both primary and secondary care in the UK and that the findings are generalisable to clinical practice in the UK.

Although the current trial demonstrated that adding bisoprolol to the routine treatments of people with COPD at high risk of exacerbation does not reduce the risk of exacerbation, as described below, the finding that bisoprolol is not associated with any clinically significant safety concerns is clinically important and directly relevant to everyday clinical practice in primary and secondary care in the UK. The BICS recruited participants with moderate/severe airflow obstruction highly likely to exacerbate, because in clinic practice these are the patients who continue to exacerbate despite maximal inhaled therapies. As evidenced by the BLOCK COPD trial, the BICS sample population is also likely to be susceptible to any respiratory side effects of beta-blockers. The absence of any clinically significant safety concerns with bisoprolol in a high-risk sample population suggests that the safety findings of BICS are relevant to people with COPD, regardless of severity and exacerbation frequency.

While the results of this trial are generalisable to the UK and probably other high-income countries, the findings may not be applicable to low/medium-income countries, with differing pharmacogenetic profiles.

Public and patient involvement

Public and patient involvement in this study was limited but effective, building on lessons learnt by the PPI of our previous study of low-dose theophylline in COPD (TWICS). A patient with COPD was an applicant on the 'outline' and 'full' proposals and in addition to being actively involved in study development, for example, feasibility, participant-facing materials, he was a member of the TSC. After our experiences of TWICS, we were keen to expand PPI and to proactively support the independent patient representative.

Chest Heart & Stroke Scotland very kindly allowed their Voices Scotland Lead to support the study. The Voices Scotland Lead recruited a panel of 15 people living with COPD from CHSS's involvement database. After training the panel of COPD volunteers, he supported them so that they were able to voice opinions and ideas. The Voices Scotland Lead was a member of the TSC, where he not only provided support for the patient representative, but also presented the opinions and ideas of the panel of COPD volunteers who had been circulated with meeting materials beforehand. The more formal support for the COPD patient representative worked well, and the panel of COPD volunteers worked extremely well, probably because they were interacting with someone they knew and who was not a medical professional. The anonymity of being represented by Voices Scotland Lead almost certainly gave the COPD panel the confidence to express their opinions in a very frank and memorable way. Unfortunately, the Voices Scotland Lead was an indirect victim of the COVID-19 pandemic; he was furloughed and subsequently made redundant.

Further support was provided by CHSS and the (then) BLF, which contributed to the application process and supported the commencement of recruitment by contributing to and publicising a press release.

Equality, diversity and inclusion

We recruited participants from both primary and secondary care sites across Scotland and England. The age and gender of participants are representative of patients living with COPD in the UK. We did not collect information on ethnicity of participants – recruitment sites served different populations. We did not have resource to offer translation of study materials, but the protocol had provision for people who were not able to read or write to be able to take part in the study if they wished. The protocol also had provision for research teams to carry out research visits at participant's homes – people with COPD often have restricted mobility because of breathing difficulties. The revisions to the protocol such that recruitment, titration and follow-up visits that could be carried out remotely may have made the study more attractive to potential participants, though it was our experience that participants attended an in-person recruitment visit. There was opportunity for junior staff to become involved in study activities that they had not previously been involved in, which will help build institutional capacity.

Conclusions

Main conclusions

This multicentre, pragmatic, double-blind, randomised, placebo-controlled trial failed to achieve its recruitment target because of COVID-19 and was underpowered. The results of this trial show that for people with COPD, at high risk of exacerbation, the addition of the beta-blocker bisoprolol to routine treatment confers no overall clinical or health economic benefit and was not associated with any clinically significant safety concerns.

Implications for practice

The trial has shown that bisoprolol does not reduce the likelihood of exacerbation in people with COPD and cannot be recommended as a treatment for COPD.

The trial has also demonstrated 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.

Recommendations for research

A systematic review with meta-analysis is planned for the clinical trials that have investigated the effectiveness and safety of beta-blockers in people with COPD. The three trials (BLOCK COPD, BICS, PACE) have all had difficulties recruiting and have closed to recruitment before achieving their recruitment target because of evidence of futility or COVID-19. It is anticipated that this study will commence in 2025.

The justification for the current study was reports from secondary analyses of observational and interventional studies of beta-blockers used for cardiovascular indications, that beta-blocker use in people with COPD was associated with reductions in exacerbations and mortality. While the current study demonstrates that bisoprolol does not reduce the likelihood of COPD exacerbation, one of the secondary analyses indicated a statistically significant reduction in COPD mortality; however, numbers were small and did not translate into a reduction in all-cause mortality. Based on these findings, a reasonable hypothesis would be that beta-blockers reduce mortality in people with COPD. To test this hypothesis, a RCT would be needed; however, the study would need to be much larger and for a longer duration than BICS, and the evidence of BICS, BLOCK COPD and PACE is that recruitment to trials of beta-blockers in people with COPD has been difficult. Nevertheless, the finding that bisoprolol is safe in people with COPD may mitigate the reluctance of people with COPD to participate.

Additional information

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Data-sharing statement

Individual de-identified participant data that underlie the results reported in this article, along with data dictionary and study protocol are available upon reasonable request. Please contact the corresponding author.

Ethics statement

The trial was approved by Scotland A Research Ethics Committee (ref 18/SS/0033) on 22 May 2018.

Information governance statement

The University of Aberdeen and NHS Grampian are committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, University of Aberdeen and NHS Grampian are joint Data Controllers, and you can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for our Data Protection Officer here: www.abdn.ac.uk/about/privacy/

Disclosure of interests

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Publications

Cotton S, Devereux G, Abbas H, Briggs A, Campbell K, Chaudhuri R, *et al.* Use of the oral beta blocker bisoprolol to reduce the rate of exacerbation in people with chronic obstructive pulmonary disease (COPD): a randomised controlled trial (BICS). *Trials* 2022;**23**:307. https://doi.org/10.1186/s13063-022-06226-8

Devereux G, Cotton S, Nath M, McMeekin N, Campbell K, Chaudhuri R, *et al.* Bisoprolol in patients with chronic obstructive pulmonary disease at high risk of exacerbation: the BICS randomized clinical trial. *JAMA* 2024;13:**332**:462–70. https://doi:10.1001/jama.2024.8771

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Appendix 1 Summary of protocol amendments

Protocol version and date	Details of changes made
1, 12 February 2018	New document
2, 30 April 2018	**Changes required by REC** • Addition of people without capacity to the exclusion criteria
3, 25 May 2018	**Changes required by MHRA** • Addition of pregnancy testing for women of childbearing age • Addition of section on contraceptive requirements • Clarification of process for reporting urgent safety measures
4, 30 May 2018	• Section 6.2 – Removal of requirement to have ECG (amended throughout protocol) • Section 7.2 – Consent received • Section 7.6 – Confirmation (at each visit) that participant is content to continue in the trial • Section 8.4 – Clarification of process for drug disposal • Section 9.11 – Clarification in relation to incidental findings • Section 11.4 – Amendment to the archiving period (25 years) • *Appendix 6* – Addition of BICS Heart Study protocol
5, 23 March 2020	**COVID-19 related** • *Appendix 7* – Addition of continency arrangements in response to COVID-19 pandemic; ceasing face-to-face contact by moving study visits to telephone calls
6, 1 December 2020	**COVID-19 related** • Summary of the three main protocol changes to allow recruitment to restart and the justification for this (Appendix 8) • Revisions to inclusion criteria (synopsis, scientific summary, trial flow chart, section 6.1, 7.1.2) • Revisions to the titration (synopsis, lay summary, scientific summary, trial flow chart, section 8.7.1, 8.7.2) • Reduction in number of face-to-face study visits and associated processes (lay summary, scientific summary, section 4, section 7.1.1, section 7.1.3, section 7.2, 7.2.2, section 7.6, section 9.6.1) • Update to secondary outcomes (synopsis, scientific summary, trial flow chart; 3.2; 3.4) • Mitigation of risk (section 2.1) **Non-COVID related** • Signature page – Addition of clinical trials pharmacist signature • Updates to membership/contact details for TSC • Section 7.2 – Addition of text in relation to patients who cannot read and/or write • Section 7.5 – Addition of text in relation to unblinding of the DMC in relation to SAEs • Section 8.4 – Reference to stability data at temperatures higher than 25 °C • Sections 8.6 and 8.7 – Relaxation of the timing around dose titration to accommodate the pragmatic nature of the study • Section 9.2 – Confirmation that pneumonia should be captured as a SAE • *Appendix 6* – Relaxation of the timing around the cardiac substudy to accommodate the pragmatic nature of the study
7, 14 May 2021	• Section 8.11 – Confirmation that during pandemics participants should return unused medication to a local pharmacy for destruction • Section 13.9 – Confirmation that digital sphygmomanometers will be provided to sites for participants to assess their heart rate and blood pressure at home • *Appendix 1* – Addition of statement confirming no interaction between COVID vaccines and the study medication • *Appendix 6* – Addition of high-sensitivity C-reactive protein (hs-CRP) and galectin to the blood tests that will be done • Correction of minor typographical errors and inconsistencies within the protocol
8, 30 November 2022	• Section 7.12 – Update to end of funding date • Section 10.2 – Addition of text describing the impact of COVID on recruitment and confirming recruitment, follow-up and funding end dates and confirming final sample size • Section 11.4 – Addition of text to allow sites to archive paper copies of case report forms and questionnaires locally

Appendix 2 Breaches reported within the bisoprolol in chronic obstructive pulmonary disease study

Breach	Description
1	The protocol defined the window for blood samples and echocardiography for the cardiac substudy as week 3–7. In total, 14 participants had these tests out with the defined window. This was often as a result of delays in titration, for example, because of participant exacerbation. The protocol also stated that participants be approached to take part in the substudy during the dose-titration phase. Six participants consented to the main study and the substudy on the same day. The breach was assessed as non-serious because delays in the taking of blood samples or the performing of echocardiogram did not impact scientific validity of the study (used to risk stratify participants) or compromise the safety of the participants. Similarly, consenting to the main study and the cardiac substudy on the day was unlikely to have had any impact on the safety, physical or mental integrity of subjects; there was no impact of this on the scientific value of the trial.
2	At the outset of the COVID-19 pandemic in the UK, we aimed to minimise patient contact. On 16 March 2020, we informed sites that titration visits could be conducted by telephone consultation or home visit. On 19 March 2020, we issued further guidance that all face-to-face contact with patients be suspended. We provided guidance to recruitment sites on how to manage titration by telephone. We prepared an amendment to the protocol to reflect these changes which was submitted to REC and MHRA on 24 March 2020 and approved by both bodies on 26 March 2020. This breach documented the 35 participants who had a telephone titration visit before the amendment had been approved. The breach was assessed as non-serious because removing the need for face-to-face study contact was the safest approach for this patient group who were at high risk from COVID-19. This approach allowed them to continue to take the study medication and to take part in the study.
3	A delivery of study medication was made by the courier to participant 126011 who we later found out was deceased. It was not clear from the courier documentation who had received the delivery, and so the study medication could not be located for a period of time. The participant's daughter later confirmed that a neighbour had taken in the package. She was advised to take the study medication to the local pharmacy and ask them to dispose of them safely. The breach was assessed as non-serious because there was no impact on the safety or physical or mental integrity of the subjects of the trial (or the wider general public) or on the scientific value of the trial. The medication has been traced, and we have advised that it is taken to a pharmacy for safe disposal.
4	Participant 126011 who had titration to one tablet a day thought they were running low on study medication and asked their GP to prescribe bisoprolol 1.25 mg which they had done, and the participant had started taking one tablet a day. The participant later located their supply of study medication. When the event was identified, the participant had been taking their GP-prescribed bisoprolol for approximately 10 days. They were advised to stop taking the GP-prescribed medication and also not to take any of the study medication. The participant did not suffer any adverse effects from taking the prescribed bisoprolol or while weaning off this. The breach was assessed as non-serious because there was no impact on the safety or physical or mental integrity of the subjects of the trial or on the scientific value of the trial. The participant will be included in the ITT analysis, and if they meet the criteria, they will also be included in the per-protocol analysis.
5	There was a change of Principal Investigator (PI) at one of the sites during the study. A non-substantial amendment should have been processed to reflect this change. The research and development department at the site was aware of the change of the PI, but the sponsor was not aware. The breach was assessed as non-serious because there was no impact on the safety or physical or mental integrity of the subjects of the trial or on the scientific value of the trial. The participants from the site are included in the ITT analysis, and if they meet the criteria, they are also included in the per-protocol analysis.
6	During study close-out monitoring, it was noted that six participants (at three different sites) had been consented by a member of the research team who had not been delegated the task of consent. In a full review of all consent forms by the study team, three additional participants (from two different sites) were also identified. In all cases, the PI at the site confirmed that they were happy for the member of the research team to have received consent, that they were appropriately trained, and that it had been an oversight on the delegation log that the task had not been delegated. The breach was assessed as non-serious because there was no impact on the safety or physical or mental integrity of the subjects of the trial or on the scientific value of the trial. The participants from the site are included in the ITT analysis, and if they meet the criteria, they are also included in the per-protocol analysis.
7	During study close-out, it became apparent that one site had misplaced their site-file which contained original copies of the consent forms, CRFs, patient questionnaires and prescriptions. Despite extensive efforts, it has not been located. It is not clear whether it has been misplaced within the recruitment site or if it has been destroyed. The breach was assessed as non-serious because there was no impact on the safety or physical or mental integrity of the subjects of the trial or on the scientific value of the trial. The participants from the site are included in the ITT analysis, and if they meet the criteria, they are also included in the per-protocol analysis.

Appendix 3 Recruitment by site

Site name	Number of participants recruited
49 Marine Avenue Surgery	1
Aberdeen Royal Infirmary	94
Acorn Surgery	6
Aintree University Hospital	33
Alnwick Medical Group	2
Ash Trees Surgery	4
Axbridge & Wedmore Medical Practice	2
Barton Surgery	5
Bay Medical Group	5
Bedford Hospital	4
Birmingham – Heartlands Hospital	12
Birmingham – Queen Elizabeth Hospital	12
Bishopgate Medical Centre	4
Royal Blackburn Teaching Hospital	1
Blackhall & Peterlee Practice	3
Blackpool Victoria Hospital	8
The Bovey Tracey & Chudleigh Practice	6
Brunel Medical Practice	3
Carmel Medical Practice	2
Cartmel Surgery	2
Castlegate and Derwent Surgery	14
Channel View Medical Group	5
Church View Surgery	3
Claremont Medical Practice	3
Danetre Medical Practice	2
Darlington Memorial Hospital	1
The Discovery Practice	1
Doncaster Royal Infirmary	1
Freeman Hospital	10
The Garth Surgery	4
Queen Elizabeth Hospital, Gateshead	5
Gartnavel General Hospital, Glasgow	29
Haltwhistle Medical Group	2
The Haven Surgery	1
Jubilee Medical Group	2
Kingston Hospital, Kingston-upon-Thames	2
Victoria Hospital, Kirkcaldy	1
Lakenham Surgery	1

Site name	Number of participants recruited
Royal Lancaster Infirmary	1
Lancaster Medical Practice	10
Leadgate Surgery	6
Leslie Medical Practice	2
Medway Maritime Hospital	5
Musgrove Park Hospital	3
Newquay Health Centre	6
Ninewells Hospital, Dundee	22
Norfolk and Norwich University Hospitals NHS Foundation Trust	6
University Hospital of North Durham	4
University Hospital of North Tees	5
North Tyneside General Hospital	15
Oak Tree Surgery	3
Orchard Surgery	1
Paxton Medical Group	1
Peel House Medical Centre	1
Pelton & Fellrose Medical Group	3
The Peninsula Practice	3
University Hospitals Plymouth	2
Prudhoe Medical Group	2
Queen Square Medical Practice	8
Rolle Medical Partnership	3
Royal Liverpool	4
Sherwood Forest Hospitals NHS Foundation Trust	1
Skerne Medical Group	7
South Tyneside	25
Southmead Hospital	19
St Stephen's Gate Medical Practice	3
Staploe Medical Centre	6
Teign Estuary Medical Group	7
Vauxhall Health Centre	8
The Village Practice	1
Waterloo Medical Centre	11
Well Close Medical Group	3
Royal Albert Edward Infirmary, Wigan	3
Arrowe Park Hospital, Wirral	1
University Hospital Wishaw	10
York Hospital	2

Appendix 4 EuroQol-5 Dimensions, five-level version results by individual domain at baseline, 6- and 12-month follow-up

	Bisoprolol			Placebo		
	Baseline	6 months	12 months	Baseline	6 months	12 months
Domain/level						
Mobility						
No problems	37 (19.6%)	44 (23.7%)	50 (27.5%)	42 (22.2%)	53 (28.7%)	47 (26.0%)
Slight problems	42 (22.2%)	45 (24.2%)	40 (22.0%)	39 (20.6%)	42 (22.7%)	38 (21.0%)
Moderate problems	63 (33.3%)	58 (31.2%)	59 (32.4%)	61 (32.3%)	63 (34.1%)	64 (35.4%)
Severe problems	47 (24.9%)	38 (20.4%)	33 (18.1%)	46 (24.3)	26 (14.1%)	32 (17.7%)
Extreme problems	0	1 (0.5%)	0	1 (0.5%)	1 (0.5%)	0
Self-care						
No problems	88 (46.6%)	97 (52.2%)	84 (46.2%)	97 (51.3%)	94 (50.8%)	96 (53.0%)
Slight problems	51 (27.0%)	33 (17.7%)	39 (21.4%)	42 (22.2%)	46 (24.9%)	40 (22.1%)
Moderate problems	38 (20.1%)	40 (21.5%)	46 (25.3%)	36 (19.1%)	34 (18.4%)	34 (18.8%)
Severe problems	9 (4.8%)	13 (7.0%)	11 (6.0%)	14 (7.4%)	11 (6.0%)	11 (6.1%)
Extreme problems	3 (1.6%)	3 (1.6%)	2 (1.1%)	0	0	0
Usual activities						
No problems	35 (18.5%)	47 (25.3%)	46 (25.3%)	41 (21.7%)	51 (27.6%)	46 (25.4%)
Slight problems	43 (22.8%)	42 (22.6%)	38 (20.9%)	43 (22.8%)	47 (25.4%)	41 (22.7%)
Moderate problems	73 (38.6%)	59 (31.7%)	63 (34.6%)	59 (31.2%)	53 (28.7%)	61 (33.7%)
Severe problems	32 (16.9%)	24 (12.9%)	23 (12.6%)	36 (19.1%)	23 (12.4%)	23 (12.7%)
Extreme problems	6 (3.2%)	14 (7.5%)	12 (6.6%)	10 (5.3%)	11 (6.0%)	10 (5.5%)
Pain/discomfort						
No problems	72 (38.1%)	65 (35.0%)	84 (46.2%)	68 (36.0%)	79 (42.7%)	78 (43.1%)
Slight problems	39 (20.6%)	47 (25.3%)	33 (18.1%)	47 (24.9%)	39 (21.1%)	42 (23.2%)
Moderate problems	48 (25.4%)	48 (25.8%)	42 (23.1%)	49 (25.9%)	48 (26.0%)	38 (21.0%)
Severe problems	25 (13.2%)	24 (12.9%)	20 (11.0%)	20 (10.6%)	17 (9.2%)	21 (11.6%)
Extreme problems	5 (2.7%)	2 (1.1%)	3 1.7%)	5 (2.7%)	2 (1.1%)	2 (1.1%)
Anxiety/depression						
No problems	104 (55.0%)	88 (47.3%)	88 (48.4%)	95 (50.3%)	94 (50.8%)	81 (44.8%)
Slight problems	35 (18.5%)	44 (23.7%)	42 (23.1%)	44 (23.3%)	40 (21.6%)	54 (29.8%)
Moderate problems	35 (18.5%)	33 (17.7%)	41 (22.5%)	38 (20.1%)	40 (21.6%)	32 (17.7%)
Severe problems	35 (6.9%)	16 (8.6%)	9 (5.0%)	11 (5.8%)	4 (2.2%)	6 (3.3%)
Extreme problems	2 (1.1%)	5 (2.7%)	2 1.1%)	1 (0.5%)	7 (3.8%)	8 (4.4%)

Appendix 5 Events reported during the study as possible serious adverse reactions

Case ID/ subject number	Country Gender Age	Serious adverse drug reactions	Outcome	Date of onset	Suspect drug	Daily dose route formulation	Dates of treatment, treatment duration	Comments Classification[a]
SOC: Respiratory, thoracic and mediastinal disorders								
224001 (ID 023)	UK Female 66	T2 respiratory failure	Fatal	16 November 2019	n/a – placebo	3 placebo tablets, once daily	27 June 2019; ongoing at time of death	Participant unblinded and confirmed to be randomised to placebo Classification: SAE
SOC: Injury, poisoning and procedural complications								
163006 (ID 029)	UK Male 81	Fracture of base of neck of femur, closed	Unknown	26 January 2020	Bisoprolol	5 mg bisoprolol once daily	27 September 2019; ongoing at time of event	Participant unblinded and confirmed to be randomised to bisoprolol Classification: SUSAR GB-MHRA-ESUSAR-215830222001-00105665
107007 (ID 054)	UK Female 77	Fall resulting in right knee laceration	Recovering	13 December 2020	n/a – placebo	3 placebo tablets once daily	11 March 2020; ongoing at time of event	Assessment of 'expected' confirmed by PI and sponsor Allocation not unblinded until the end of study Classification: SAE
SOC: Vascular disorders								
104016 (ID 025)	UK Male 80	Postural drop (leading to fall, right wrist injury)	Unknown	10 January 2020	Bisoprolol	2.5 mg bisoprolol once daily	30 September 2019; ongoing at time of event	Participant unblinded and confirmed to be randomised to bisoprolol Classification: SUSAR GB-MHRA-ESUSAR-215830222001-00105643
104024 (ID 077)	UK Male 91	Orthostatic hypotension	Recovered		n/a – placebo	4 placebo tablets once daily	1 June 2022; ongoing at time of event	Assessment of 'expected' confirmed by PI and sponsor Allocation not unblinded until the end of study Classification: SAE
SOC: Nervous system disorders								
101088 (ID 083)	UK Male 83	Vertigo-labyrinthitis, poor mobility	Recovered with sequelae	25 Mar 2023	n/a – placebo	4 placebo tablets once daily	2 May 2022; ongoing at time of event	Participant unblinded and confirmed to be randomised to placebo Classification: SAE

PI, Principal Investigator.

a All these events were initially reported by the site as a potential SAR. Two were unexpected, unblinded and were confirmed to be allocated to bisoprolol – and so were classified as SUSAR. Two were unexpected, unblinded and were confirmed to be allocated to placebo – and so were classified as SAE. Two were initially reported by the site as expected and so were not unblinded until the end of the study. Both were confirmed to be allocated to placebo – and so were reclassified as SAE.

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Appendix 6 Serious adverse events

Case ID/subject number	Country Gender Age	SAE	Outcome	Date of onset	Suspect drug	Daily dose Route formulation ALLOCATION – unblinded at end of study	Dates of treatment, treatment duration	Comments
SOC: Respiratory, thoracic and mediastinal disorders								
102010 (ID 001)	UK Male 53	Pneumothorax	Recovering	25 April 2019	No	2.5 mg bisoprolol or placebo once daily PLACEBO	4 April 2019; ongoing	None
101032 (ID 007)	UK Male 74	Exacerbation of COPD	Fatal	14 August 2019	No	1.25 mg bisoprolol or placebo once daily PLACEBO	19 July 2019; ongoing at time of death	None
126004 (ID 010)	UK Female 70	COPD	Fatal	16 August 2019	No	n/a – had ceased study medication 25 June 2019 PLACEBO	30 April 2019–25 June 2019	None
101023 (ID 012)	UK Female 56	Exacerbation of COPD	Fatal	23 September 2019	No	n/a – had ceased study medication 15 May 2019 PLACEBO	5 April 2019–15 May 2019	None
102019 (ID 022)	UK Male 74	Haemoptysis	Recovering	15 December 2019	No	5 mg bisoprolol or placebo once daily PLACEBO	26 July 2019; ongoing at time of event	None
110004 (ID 034)	UK Male 66	Cause of death – infective exacerbation of COPD	Fatal	1 March 2020	Not yet assessed	3.75 mg bisoprolol or placebo once daily BISOPROLOL	5 March 2019; ongoing at date of death	None
102021 (ID 047)	UK Female 66	COPD exacerbation	Fatal	4 August 2020	No	5 mg bisoprolol or placebo once daily BISOPROLOL	25 September 2019	None
240008 (ID 051)	UK Female 64	End-stage COPD	Fatal	31 August 2020	No	3.75 bisoprolol or placebo once daily PLACEBO	16 October 2019; ceased 31 August 2020	None
103007 (ID 056)	UK Female 65	Pleurisy	Recovered	25 January 2021	No	5 mg bisoprolol or placebo once daily PLACEBO	29 January 2020; ongoing at time of event	None
102014 (ID 057)	UK Female 71	COPD exacerbation	Fatal	30 March 2020	No	1.25 mg bisoprolol or placebo once daily PLACEBO	20 June 2019 to 1 July 2019	None
101066 (ID 068)	UK Male 77	Non-ST-elevation myocardial infarction, severe COPD	Fatal	12 March 2022	No	2.5 mg bisoprolol or placebo once daily PLACEBO	8 November 2021; ongoing at time of event	None
103009 (ID 070)	UK Male 78	Pulmonary embolism in both lungs	Recovered	21 March 2022	No	1.25 mg bisoprolol or placebo once daily BISOPROLOL	8 December 2021; ongoing at time of event	None
101082 (ID 076)	UK Female 58	Severe COPD and acute broncho-pneumonia	Fatal	3 June 2022	No	5 mg bisoprolol or placebo once daily PLACEBO	23 March 2022; ongoing at time of event	None
351003 (ID 075)	UK Female 74	Cause of death – acute exacerba-tion of COPD	Fatal	18 August 2022	No	5 mg bisoprolol or placebo once daily PLACEBO	11 April 2022; ongoing at time of event	None

Case ID/subject number	Country Gender Age	SAE	Outcome	Date of onset	Suspect drug	Daily dose Route formulation ALLOCATION – unblinded at end of study	Dates of treatment, treatment duration	Comments
351005 (ID 079)	UK Male 79	Infrequent exacerbation of COPD with emphysematous bullae in right hemithorax	Recovered with sequelae	18 November 2022	No	3.75 mg bisoprolol or placebo once daily BISOPROLOL	25 May 2022; ongoing at time of event	None
SOC: Neoplasms benign, malignant and unspecified (including cysts and polyps)								
170001 (ref 002)	UK Female 72	Brain tumour	Not recovered	16 May 2019	No	2.5 mg bisoprolol or placebo once daily PLACEBO	27 February 2019; ongoing	None
121008 (ID 011)	UK Female 61	Triple negative breast cancer with liver/lung/ spleen and mediastinum metastases	Fatal	3 June 2019	No	5 mg bisoprolol or placebo once daily BISOPROLOL	15 March 2019; ongoing at time of event	None
166001 (ID 026)	UK Female 63	Malignant tumour of the lung	Fatal	15 December 2019	No	5 mg bisoprolol or placebo once daily BISOPROLOL	12 April 2019; ongoing at time of event	None
101013 (ID 028)	UK Female 50	Left breast cancer	Unknown	27 January 2020	No	5 mg bisoprolol or placebo once daily BISOPROLOL	7 February 2019; ongoing at time of event	None
101020 (ID 035)	UK Male 80	Lung cancer	Unknown	7 September 2019	No	5 mg bisoprolol or placebo once daily PLACEBO	29 March 2019; ongoing at time of event	None
101040 (ID 040)	UK Female 78	Small cell lung carcinoma	Fatal	1 April 2020	No	3.75 mg bisoprolol or placebo once daily PLACEBO	16 October 2019; ongoing at time of event	None
121015 (ID 043)	UK Female 66	Endometrial carcinoma	Not recovered	3 December 2019	No	2.5 mg bisoprolol or placebo once daily PLACEBO	29 May 2019; ongoing at time of event	None
240018 (ID 046)	UK Male 70	Metastatic stomach cancer	Fatal	4 June 2020	No	2.5 mg bisoprolol or placebo once daily BISOPROLOL	25 February 2020; ongoing at date of death	None
177013 (ID 045)	UK Female 58	Malignant neoplasm lung	Fatal	21 July 2020	No	5 mg bisoprolol or placebo once daily PLACEBO	12 July 2019; ongoing at time of event	Final outcome was fatal; death was out with the 1-year follow-up period; not included in *Table 12*
177020 (ID 055)	UK Male 62	Metastatic small cell lung cancer	Fatal	7 October 2020	No	2.5 mg bisoprolol or placebo once daily PLACEBO	11 December 2019; ongoing at time of event	None
311004 (ID 065)	UK Male 59	Lung cancer	Fatal	16 February 2022	No	2.5 mg bisoprolol or placebo once daily PLACEBO	14 January 2022; ongoing at time of event	None

continued

Case ID/subject number	Country Gender Age	SAE	Outcome	Date of onset	Suspect drug	Daily dose Route formulation ALLOCATION – unblinded at end of study	Dates of treatment, treatment duration	Comments
SOC: Musculoskeletal and connective tissue disorders								
125005 (ID 005)	UK Female 71	Muscular pain	Recovering	17 June 2019	No	n/a – had not commenced study medication PLACEBO	n/a – had not commenced study medication	None
SOC: Cardiac disorders								
107001 (ID 006)	UK Female 70	Angina	Recovered	22 July 2019	No	5 mg bisoprolol or placebo once daily BISOPROLOL	13 November 2018; ongoing at time of event	None
105013 (ID 013)	UK Female 68	Acute ST segment elevation myocardial infarction	Recovering	7 September 2019	No	1.25 mg bisoprolol or placebo once daily BISOPROLOL	9 April 2019; ongoing at time of event	None
247001 (ID 031)	UK Male 76	Atrial flutter	Fatal	10 February 2020	No	1.25 mg bisoprolol or placebo once daily BISOPROLOL	23 January 2020; ongoing at time of event	None
177019 (ID 052)	UK Female 72	Fast atrial fibrillation	Recovering	19 October 2020	No	2.5 mg bisoprolol or placebo once daily BISOPROLOL	27 November 2019; ongoing at time of event	None
177019 (ID 060)	UK Female 72	Fast atrial fibrillation	Recovered	13 November 2020	No	2.5 mg bisoprolol or placebo once daily BISOPROLOL	27 November 2019; ongoing at time of event	None
351001 (ID 064)	UK Female 65	Decompensated heart failure, headache, low INR	Recovered	15 February 2022	No	3.75 mg bisoprolol or placebo once daily PLACEBO	14 January 2022; ongoing at time of event	None
291001 (ID 074)	UK Male 59	Hypertension, paroxysmal atrial fibrillation	Recovered with sequelae	6 July 2022	No	5 mg bisoprolol or placebo once daily PLACEBO	3 February 2021 ongoing at time of event	None
102032 (ID 080)	UK Female 67	Infective exacerbation COPD with new fast atrial fibrillation	Recovered with sequelae	24 December 2022	No	5 mg bisoprolol or placebo once daily BISOPROLOL	12 April 2022; ongoing at time of event	None
102033 (ID 084)	UK Male 66	Right heart failure	Recovered	21 March 2023	No	1.25 mg bisoprolol or placebo once daily BISOPROLOL	6 April 2022; ongoing at time of event	None
SOC: Vascular disorders								
174001 (ID 049)	UK Male 68	Cor pulmonale	Recovered	29 September 2020	No	2.5 mg bisoprolol or placebo once daily PLACEBO	11 February 2019; ongoing at time of event	None
SOC: Nervous system disorders								
101026 (ID 008)	UK Male 84	Stroke	Fatal	1 September 2019	No	1.25 mg bisoprolol or placebo once daily BISOPROLOL	16 May 2019; ongoing at time of event	None
101011 (ID 014)	UK Male 76	Transient ischaemic attack(TIA)	Recovering	25 September 2019	No	1.25 mg bisoprolol or placebo once daily BISOPROLOL	15 January 2019; ongoing at time of event	None

Case ID/subject number	Country Gender Age	SAE	Outcome	Date of onset	Suspect drug	Daily dose Route formulation ALLOCATION – unblinded at end of study	Dates of treatment, treatment duration	Comments
169004 (ID 048)	UK Male 76	Posterior circulation TIA	Recovered	29 July 2020	No	5 mg bisoprolol or placebo once daily PLACEBO	24 September 2019; ongoing at time of event	None
101063 (ID 071)	UK Female 71	TIA	Recovered	21 May 2022	No	5 mg bisoprolol or placebo once daily BISOPROLOL	12 October 2021; ongoing at time of event	None
101085 (ID 081)	UK Female 74	Worsening shortness of breath and bilateral paraesthesia	Recovered with sequelae	7 December 2022	No	5 mg bisoprolol or placebo once daily BISOPROLOL	5 April 2022; ongoing at time of event	None
SOC: Gastrointestinal disorders								
163003 (ID 009)	UK Female 73	Bowel obstruction	Unknown	5 September 2019	No	n/a – had not commenced study medication BISOPROLOL	n/a – had not commenced study medication	None
101003 (ID 019)	UK Female 74	Colon inflammation	Recovering	30 October 2019	No	5 mg bisoprolol or placebo once daily PLACEBO	22 September 2018; ongoing at time of event	None
101045 (ID 033)	UK Female 59	Pancreatitis	Recovered with sequelae	28 February 2020	No	5 mg bisoprolol or placebo once daily BISOPROLOL	22 November 2019; ongoing at time of event	None
101045 (ID 037)	UK Female 59	Necrotising pancreatitis	Fatal	15 March 2020	No	5 mg bisoprolol or placebo once daily BISOPROLOL	22 November 2019; ongoing at time of event	None
124003 (ID 038)	UK Male 70	Bowel perforation	Fatal	7 March 2020	No	n/a had ceased study medication 18 June 2019 BISOPROLOL	15 May 2019 to 18 June 2019	None
126003 (ID 042)	UK Male 68	Acute enterocolitis	Recovered with sequelae	22 April 2020	No	2.5 mg bisoprolol or placebo once daily PLACEBO	25 April 2019; ongoing at time of event	None
121008 (ID 059)	UK Female 62	Abdominal pain and vomiting (likely constipation)	Recovered	3 January 2020	No	5 mg bisoprolol or placebo once daily BISOPROLOL	15 March 2019; ongoing at time of event	None
311001 (ID 066)	UK Male 71	Pancreatitis	Unknown	15 March 2022	No	1.25 mg bisoprolol or placebo once daily BISOPROLOL	21 September 2021; ongoing at time of event	None
311001 (ID 072)	UK Male 71	Cholecystitis, liver microabscesses and mild pancreatitis	Recovered	25 April 2022	No	1.25 mg bisoprolol or placebo once daily BISOPROLOL	21 September 2021; ongoing at time of event	None
SOC: Infections and infestations								
102011 (ID 003)	UK Male 64	Double pneumonia	Recovering	25 May 2019	No	3.75 mg bisoprolol or placebo once daily BISOPROLOL	26 April 2019; ongoing	None
101026 (ID 004)	UK Male 84	Pneumonia	Recovered	26 May 2019	No	1.25 mg bisoprolol or placebo once daily BISOPROLOL	16 May 2019; ongoing	None

continued

Case ID/subject number	Country Gender Age	SAE	Outcome	Date of onset	Suspect drug	Daily dose Route formulation ALLOCATION – unblinded at end of study	Dates of treatment, treatment duration	Comments
124005 (ID 015)	UK Male 63	Urinary tract infection	Recovered	29 September 2019	No	2.5 mg bisoprolol or placebo once daily PLACEBO	11 September 2019; ongoing at time of event	None
246001 (ID 018)	UK Female 76	Influenza	Recovering	16 November 2019	No	3.75 mg bisoprolol or placebo once daily PLACEBO	10 October 2019; ongoing at time of event	None
101036 (ID 020)	UK Female 76	Left basal pneumonia	Recovered	2 December 2019	No	3.75 mg bisoprolol or placebo once daily BISOPROLOL	5 September 2019; ongoing at time of event	None
101012 (ID 024)	UK Female 73	Pneumonia	Recovered	12 October 2019	No	5 mg bisoprolol or placebo once daily; BISOPROLOL	31 January 2019; ongoing at time of event	None
217004 (ID 027)	UK Male 79	Influenza	Recovering	21 December 2019	No	2.5 mg bisoprolol or placebo once daily; BISOPROLOL	13 September 2019; ongoing at time of event	None
240012 (ID 039)	UK Female 73	Coronavirus disease 2019	Recovered	31 March 2020	No	5 mg bisoprolol or placebo once daily; PLACEBO	20 November 2019; ongoing at time of event	None
103006 (ID 050)	UK Female 64	Cellulitis (left leg)	Recovered	5 August 2020	No	2.5 mg bisoprolol or placebo once daily PLACEBO	13 November 2019; ongoing at time of event	None
177004 (ID 053)	UK Female 75	Herpes simplex of the eye	Recovered	2 March 2020	Not yet assessed by site	2.5 mg bisoprolol or placebo once daily BISOPROLOL	2 May 2019; ongoing at time of event	None
101060 (ID 061)	UK Male 74	Clostri dium difficile and acute kidney injury	Recovered	8 November 2021	No	5 mg bisoprolol or placebo once daily BISOPROLOL	22 September 2021; ongoing at time of event	None
154010 (ID 062)	UK Male 84	Dyspnoea due to ongoing COVID symptoms Renal failure with acidosis, upper GI bleed	Recovered	17 January 2022	No	5 mg bisoprolol or placebo once daily PLACEBO	8 November 2021; ongoing at time of event	None
101062 (ID 067)	UK Female 53	Pneumonia	Recovered	30 January 2022	No	5 mg bisoprolol or placebo once daily PLACEBO	11 October 2021; ongoing at time of event	None
351002 (ID 069)	UK Female 56	Community-acquired pneumonia	Recovered	24 April 2022	No	3.75 mg bisoprolol or placebo once daily BISOPROLOL	11 February 2022; ongoing at time of event	None
101063 (ID 073)	UK Female 71	Right basal pneumonia, atrial fibrillation	Recovered	5 July 2022	No	5 mg bisoprolol or placebo once daily BISOPROLOL	12 October 2021; ongoing at time of event	None
101085 (ID 082)	UK Female 74	Pneumonia	Fatal	13 February 2023	No	5 mg bisoprolol or placebo once daily BISOPROLOL	5 April 2022; ongoing at time of event	None
SOC: Blood and lymphatic system disorders								
101072 (ID 063)	UK Male 78	Significant anaemia	Recovered	20 February 2022	No	2.5 mg bisoprolol or placebo once daily PLACEBO	16 December 2021; ongoing at time of event	None

Case ID/subject number	Country Gender Age	SAE	Outcome	Date of onset	Suspect drug	Daily dose Route formulation ALLOCATION – unblinded at end of study	Dates of treatment, treatment duration	Comments
SOC: Psychiatric disorders								
126014 (ID 058)	UK Male 59	Admission to mental health hospital – no further details	Unknown	Approx June 2020	No	3.75 mg bisoprolol or placebo once daily BISOPROLOL	12 November 2019; unknown if ongoing at time of event	No further details could be obtained for the event, assessed as unlikely to be related on the limited information available
247003 (ID 078)	UK Female 61	Suicide	Fatal	21 October 2022	No	2.5 mg bisoprolol or placebo once daily PLACEBO	12 November 2021; ongoing at time of event	None
SOC: Injury, poisoning and procedural complications								
182002 (ID 016)	UK Male 70	Overdose (paracetamol)	Recovered	29 August 2019	No	1.25 mg bisoprolol or placebo once daily BISOPROLOL	23 May 2019; ongoing at time of event	None
101036 (ID 017)	UK Female 87	Hip fracture	Recovering	4 October 2019	No	3.75 mg bisoprolol or placebo once daily BISOPROLOL	5 May 2019; ongoing at time of event	None
112003 (ID 030)	UK Male 71	Rib fracture	Recovering	7 February 2020	No	1.25 mg bisoprolol or placebo once daily BISOPROLOL	24 January 2019	None
177003 (ID 041)	UK Female 71	Laceration of head	Recovered	17 January 2020	No	1.25 mg bisoprolol or placebo once daily BISOPROLOL	30 April 2019; ongoing at time of event	None
240001 (ID 044)	UK Female 86	Multiple injuries sustained following fall	Fatal	23 March 2020	No	n/a had ceased study medication 28 August 2019 BISOPROLOL	24 July 2019 to 28 August 2019	None
SOC: General disorders and administration site conditions								
121017 (ID 021)	UK Male 71	Non-cardiac chest pain	Recovered	27 June 2019	No	n/a had ceased study medication 25 June 2019 BISOPROLOL	6 June 2019 to 25 June 2019	None
SOC: Metabolism and nutrition disorders								
131003 (ID 032)	UK Male 74	Diuretic and PPI-induced hyponatraemia	Recovered	17 December 2019	No	1.25 mg bisoprolol or placebo once daily BISOPROLOL	4 November 2019; ongoing at time of event	None
SOC: Renal and urinary disorders								
155002 (ID 036)	UK Male 75	Urinary retention due to enlarged prostate	Recovered with sequelae	1 March 2020	No	5 mg bisoprolol or placebo once daily BISOPROLOL	20 March 2019; ongoing at time of event	None

Appendix 7 Subgroup analysis

Category		Bisoprolol	Placebo	IRR[a]	Lower CI	Upper CI	Interaction *p*-value
All participants	*N*	259	256				
	Mean	2.02	2.00				
	SD	1.91	1.75	0.97	0.83	1.12	0.66
Sex							
Female	*N*	125	116				
	Mean	2.18	1.89				
	SD	1.89	1.81	1.05	0.85	1.31	0.647
Male	*N*	134	140				
	Mean	1.87	2.10				
	SD	1.91	1.70	0.89	0.72	1.10	0.289
Age group							
< 60 years	*N*	43	39				
	Mean	1.93	2.10				
	SD	2.11	1.87	1.07	0.73	1.56	0.740
60–69 years	*N*	97	113				
	Mean	2.01	2.11				
	SD	1.81	1.80	0.88	0.69	1.11	0.278
70–79 years	*N*	106	89				
	Mean	2.10	1.94				
	SD	1.95	1.70	1.00	0.78	1.28	0.987
80+ years	*N*	13	15				
	Mean	1.77	1.33				
	SD	1.69	1.23	1.13	0.56	2.28	0.732
Smoking status							
Current	*N*	78	82				
	Mean	2.05	2.12				
	SD	1.76	1.70	0.91	0.69	1.19	0.478
Ex-smoker	*N*	181	174				
	Mean	2.01	1.95				
	SD	1.97	1.77	0.99	0.83	1.19	0.953
BMI category							
Underweight	*N*	15	19				
	Mean	2.60	2.32				
	SD	1.50	1.45	0.79	0.45	1.37	0.395

Category		Bisoprolol	Placebo	IRR[a]	Lower CI	Upper CI	Interaction *p*-value
Normal	*N*	89	90				
	Mean	1.97	1.96				
	SD	1.96	1.87	1.04	0.80	1.34	0.787
Overweight	*N*	97	67				
	Mean	2.30	2.25				
	SD	2.07	1.74	0.95	0.73	1.23	0.690
Obese	*N*	57	78				
	Mean	1.51	1.74				
	SD	1.51	1.69	0.83	0.60	1.14	0.257
ICS at baseline							
No	*N*	44	51				
	Mean	1.50	1.80				
	SD	1.77	1.54	0.79	0.54	1.16	0.227
Yes	*N*	215	205				
	Mean	2.13	2.05				
	SD	1.92	1.80	1.00	0.85	1.18	0.966
LABA at baseline							
No	*N*	47	62				
	Mean	1.53	1.68				
	SD	1.80	1.52	0.80	0.56	1.14	0.214
Yes	*N*	212	194				
	Mean	2.13	2.11				
	SD	1.92	1.81	1.01	0.85	1.19	0.931
LAMA at baseline							
No	*N*	32	23				
	Mean	1.75	2.09				
	SD	2.09	1.86	0.75	0.47	1.21	0.245
Yes	*N*	227	233				
	Mean	2.06	2.00				
	SD	1.88	1.74	0.99	0.85	1.16	0.932
Number of exacerbations in 12 months prior to recruitment							
2	*N*	99	102				
	Mean	1.51	1.40				
	SD	1.58	1.48	1.00	0.77	1.30	0.994
3–4	*N*	103	103				
	Mean	1.91	2.16				

continued

Category		Bisoprolol	Placebo	IRR[a]	Lower CI	Upper CI	Interaction *p*-value
	SD	1.79	1.68	0.80	0.63	1.01	0.063
5+	*N*	57	51				
	Mean	3.12	2.90				
	SD	2.19	1.95	1.10	0.83	1.46	0.516
Exacerbations in 12 months prior to recruitment requiring admission							
Yes	*N*	191	183				
	Mean	1.94	1.84				
	SD	1.87	1.67	0.92	0.76	1.10	0.342
No	*N*	68	73				
	Mean	2.26	2.42				
	SD	2.01	1.89	1.10	0.84	1.46	0.485
GOLD Stage Original							
Mild	*N*	16	12				
	Mean	1.12	0.92				
	SD	1.45	1.31	1.05	0.45	2.45	0.913
Moderate	*N*	100	124				
	Mean	1.75	1.80				
	SD	1.77	1.64	0.91	0.72	1.16	0.456
Severe	*N*	99	79				
	Mean	2.09	2.06				
	SD	2.04	1.67	0.99	0.77	1.27	0.934
Very severe	*N*	43	41				
	Mean	2.79	2.83				
	SD	1.81	2.04	1.05	0.75	1.47	0.774
GOLD 2011 Stage							
C	*N*	15	13				
	Mean	0.80	1.54				
	SD	0.77	1.56	0.46	0.20	1.05	0.065
D	*N*	244	243				
	Mean	2.10	2.03				
	SD	1.93	1.76	0.99	0.85	1.15	0.913
Oral corticosteroids at baseline							
No	*N*	85	86				
	Mean	0.61	0.76				
	SD	1.18	1.46	0.72	0.49	1.05	0.087
Yes	*N*	174	170				
	Mean	2.71	2.64				
	SD	1.81	1.53	1.01	0.88	1.16	0.889

Category		Bisoprolol	Placebo	IRR[a]	Lower CI	Upper CI	Interaction *p*-value
BDI							
Low	*N*	97	89				
	Mean	2.39	2.35				
	SD	1.90	1.85	1.03	0.81	1.31	0.801
High	*N*	155	155				
	Mean	1.81	1.79				
	SD	1.89	1.68	0.94	0.76	1.15	0.548
Dose of bisoprolol							
Fixed on 0 tablet/day	*N*	46	41				
	Mean	2.17	2.56				
	SD	2.17	2.21	0.83	0.59	1.17	0.278
Fixed on 1 tablet/day	*N*	62	28				
	Mean	2.36	2.21				
	SD	2.15	2.01	1.03	0.71	1.49	0.876
Fixed on 2 tablets/day	*N*	41	43				
	Mean	2.27	1.93				
	SD	1.88	1.61	1.10	0.77	1.58	0.606
Fixed on 3 tablets/day	*N*	37	32				
	Mean	1.92	2.50				
	SD	1.57	1.78	0.72	0.48	1.07	0.102
Fixed on 4 tablets/day	*N*	71	110				
	Mean	1.61	1.64				
	SD	1.61	1.44	0.97	0.73	1.27	0.806

BMI, body mass index; CI, confidence interval; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; IRR, incidence rate ratio; LABA, long-acting beta2 agonist; LAMA, long-acting muscarinic antagonist; µg, microgram; SD, standard deviation.

a Adjusted for: centre (as a random effect), recruitment setting (primary or secondary care), age centred on the mean, sex (male/female), smoking status (current vs. ex), FEV_1% predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long-term antibiotics.

EME
HSDR
HTA
PGfAR
PHR

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