Bisoprolol in Patients With COPD at High Risk of Exacerbation

The BICS Randomized Clinical Trial

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Key points

Question: For people with COPD at high-risk of exacerbations, does bisoprolol reduce the number of COPD exacerbations?

Finding: In this randomized double-blind placebo-controlled trial of 515 people with COPD, the number of exacerbations requiring treatment with oral corticosteroids and/or antibiotics did not differ significantly with use of bisoprolol (mean exacerbations 2.03/year) vs placebo (mean exacerbations 2.01/year).

Meaning: Treatment with bisoprolol did not reduce COPD exacerbations requiring treatment with oral corticosteroids and/or antibiotics.

Abstract

Importance: Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide. Observational studies report that β-blocker use may be associated with reduced risk of COPD exacerbations. However, a recent trial reported that metoprolol did not reduce COPD exacerbations and increased COPD exacerbations requiring hospital admission.

Objective: To test whether bisoprolol decreased COPD exacerbations in people with COPD at high risk of exacerbations.

Design, Setting and Participants: The Bisoprolol in COPD Study (BICS) was a double-blind placebo-controlled randomized clinical trial conducted in 76 UK sites (45 primary care clinics and 31 secondary clinics). Patients with COPD who had at least moderate airflow obstruction on spirometry (FEV_1/FVC <0.7, FEV_1 <80% predicted) and ≥2 COPD exacerbations treated with oral corticosteroids and/or antibiotics in the prior 12 months were enrolled from October 17, 2018, to May 31, 2022. Follow-up concluded on April 18, 2023.

Interventions: Patients were randomly assigned to bisoprolol (n=261) or placebo (n=258). Bisoprolol was started at 1.25 mg orally daily and was titrated as tolerated over 4 sessions to a maximum dose of 5 mg/d using a standardized protocol.

Main outcomes and Measures: The primary clinical outcome was the number of patient-reported COPD exacerbations treated with oral corticosteroids and/or antibiotics over the 1-year treatment period. Safety outcomes included serious adverse events and adverse reactions.

Results: Although the trial planned to enroll 1574 patients, recruitment was suspended from March, 16, 2020, to July 31, 2021, due to the COVID-19 pandemic. Two patients in each group were excluded post randomization. Among the 515 patients (mean age, 68 years; men,

274 [53%]; mean $FEV_{1,}$ 50.1%, primary outcome data were available for 514 (99.8%) and 371 (72%) remained on study drug. The primary outcome of patient-reported COPD exacerbations treated with oral corticosteroids and/or antibiotics was 526 in bisoprolol group, with a mean exacerbation rate of 2.03/year vs 513 exacerbations in the placebo group with a mean exacerbation rate of 2.01/year, adjusted incidence rate ratio (IRR) [95% CI, 0.97 (0.84, 1.13), p=0.72]. Serious adverse events occurred in 37 (14.5%) of the bisoprolol group vs 36 (14.3%) in the placebo group, [relative risk 1.01 95% CI, 0.62, 1.66), p=0.96].

Conclusions and Relevance: Among people with COPD at high risk of exacerbation, treatment with bisoprolol did not reduce the number of self-reported COPD exacerbations requiring treatment with oral corticosteroids and/or antibiotics.

Trial registration: ISRCTN10497306 https://www.isrctn.com/ISRCTN10497306

Introduction

Chronic obstructive pulmonary disease (COPD) is the world's third leading cause of death and sixth leading cause of disability.[1,2] COPD exacerbations are associated with reduced quality of life, increased mortality, lost productivity and are key drivers of healthcare costs.[3-5] Interventions to reduce exacerbations of COPD, especially those resulting in hospitalization are rated by patients as most important, above symptom relief and adverse effects of intervention.[6]

Beta-blockers reduce morbidity and mortality in people with ischemic heart disease and heart failure.[7,8] Reports from secondary analyses of observational and interventional studies of beta-blockers used for cardiovascular indications have shown that β_1-selective beta-blockers are well tolerated in patients with COPD and their use has been associated with reductions in exacerbations and mortality.[9-14] However, the recent BLOCK-COPD (beta-blockers for the prevention of acute exacerbations of COPD) trial terminated recruitment after a planned interim analysis indicated futility with respect to the primary outcome of decreased COPD exacerbations, but also raised safety concerns because metoprolol was associated with a significant twofold increased risk of exacerbation requiring hospitalization. Although metoprolol was not associated with a significant increase in mortality, the majority of deaths in the metoprolol group were attributed to COPD.[15]

The bisoprolol in COPD study (BICS) tested the hypothesis that addition of the β_1-selective beta-blocker bisoprolol to treatment of people with COPD at high risk of exacerbation, reduced the rate of moderate-severe COPD exacerbations.

Methods

Trial design and oversight

This was a double-blind placebo-controlled randomized multicenter clinical trial comparing the addition of bisoprolol or placebo to current therapy in people with COPD at high risk of exacerbation. The protocol has been published[16] and is available with the Statistical Analysis Plan in the online supplement.

The trial was approved by Scotland A Research Ethics Committee (18/SS/0033) and the Medicines and Healthcare products Regulatory Agency (EudraCT 2017-002779-24). All participants provided written informed consent.

The National Institute for Health Research Health Technology Assessment programme funded the trial.

Study Population

Patients were recruited from 76 UK sites (45 primary care clinics and 31 secondary care clinics) in the UK. In primary care, patients were identified from electronic patient records and community COPD services records. In secondary care, participants were identified from in-patient and out-patient records. Patients were eligible if they were aged ≥40 years with COPD and at least moderate airflow obstruction [ratio forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC)<0.7, and FEV_1<80% predicted],[17] >10 pack year smoking history, and ≥2 exacerbations treated with oral corticosteroids and/or antibiotics in the previous year. Exclusion criteria included: a diagnosis of asthma before age 40 years, resting heart rate <60 /min, systolic blood pressure <100 mmHg, interacting drugs such as calcium channel blockers, class-I antiarrhythmic drugs and centrally acting antihypertensive medications (eg, clonidine), or conditions for which beta-blockers are guideline recommended (eg, heart failure, recent acute coronary syndrome). [7,8] The full list of inclusion and exclusion criteria is documented in the protocol.[16]

Study Design.

Participants were randomized 1:1 to bisoprolol or placebo groups using an internet-based randomization service created and administered by the Centre for Healthcare Randomised Trials, University of Aberdeen. The allocation sequence was generated using randomly generated blocks of entries of varying sizes permuted for each combination of center and recruitment setting. Participants were stratified by center, and clinic type (primary or secondary care). All trial participants, clinicians, outcome assessors, trial managers, and data analysts were blinded to allocation status until database lock.

Treatment Protocol

Patients were treated with bisoprolol (using 1.25mg tablets) or visually identical placebo tablets, both manufactured by Tiofarma B.V (Oud-Beijerland, Netherlands), for 52 weeks. Study drug was started at 1.25mg once daily and up-titrated, as tolerated over four titration assessments over approximately seven weeks. Dose-titration was based on heart failure guideline advice to 'start low, go slow' and a computerized advisory titration algorithm was incorporated into the study website.[18,19] Dose-titration decisions were made based on intolerable side effects (eg, fatigue), heart rate, systolic blood pressure and FEV_1 (eFigure 1). After titration was completed, patients continued a fixed dose of once daily bisoprolol of 1.25mg, 2.50mg, 3.75mg or 5mg, or placebo equivalent for the remainder of the 52-week treatment period, after which the study medication was titrated off.

Outcomes

The primary outcome was patient-reported number of COPD exacerbations treated with oral corticosteroids and/or antibiotics during the 52-week treatment period.[20] At least 2 weeks between exacerbations was necessary to be considered as separate events.[20] Outcome data were collected at baseline, 26 and 52 weeks.

The 10 clinical secondary outcomes were: number of COPD exacerbations requiring hospital admission; time to first COPD exacerbation; number of emergency hospital admissions unrelated to COPD; COPD related health status (COPD Assessment Test [CAT], scale 0-40, higher scores indicative of greater impact of COPD on health and wellbeing, minimal clinically important difference [MCID], 2 units);[21] breathlessness assessed using the Baseline Dyspnea Index (BDI) (scale 0-12, lower scores indicative of worse breathlessness) and subsequent changes by the Transition Dyspnea Index (TDI) (scale -9 to +9, lower scores indicative of greater deterioration in breathlessness, MCID, 1 unit);[22,23] post-bronchodilator spirometry conducted to American Thoracic Society/European Respiratory Society Guidelines. (FEV_1, FVC as percent predicted);[24] number of major adverse cardiovascular events (MACE);[25] COPD related mortality; all-cause mortality; and in self-selected centres, the Hull Airways Reflux Questionnaire (HARQ) was used to assess symptoms not elucidated by the CAT or dyspnea index.[26]

Safety outcomes were serious adverse events and adverse reactions.[27]

COVID-19

COVID-19 resulted in a 16-month suspension of recruitment (March 16, 2020 to July 31, 2021). In the UK during the COVID-19 pandemic, people with COPD were considered at 'high-risk' of severe outcomes with COVID-19 infection and were advised not to leave their homes and to minimize face-to-face contact. Therefore, the trial protocol was modified during that time period so that all in-person assessments were replaced by telephone or video calls. When recruitment restarted, spirometry was not possible because of closure of pulmonary function laboratories and the most recent lung function results were used to determine if patients met study inclusion criteria. For dose-titration of bisoprolol, patient report of worsening breathlessness replaced $FEV_{1,}$ and blood pressure and pulse were

measured by patients at home using digital sphygmomanometers provided by the study. The absence of in-person encounters prevented pill-counting to assess adherence; instead participants were queried about study medication adherence during video or telephone calls and were asked whether they had taken greater than or less than 70% of daily doses of study medication.

Sample Size Calculation

A previous study indicated that for people with COPD and ≥2 self-reported exacerbations in a year, the mean (standard deviation [SD]) number of COPD exacerbations in the following year was 2.22 (1.86).[28] Assuming a similar rate in the placebo arm, 669 participants were needed in each trial arm to detect a 15% reduction in exacerbations (i.e. from 2.22 to 1.89) with 90% power at the two-sided 5% alpha error. Allowing for 15% withdrawal from study treatment, 787 participants were required in each treatment group (i.e. 1574 in total). The proposed treatment effect of a 15% reduction in exacerbations was based upon a trial of low dose theophylline in COPD (TWICS), which was determined after consultation with primary and secondary care clinicians, who considered a 15% reduction in COPD exacerbations to be a small but clinically important outcome.[29]

Statistical Analysis

All analyses were governed by a Statistical Analysis Plan and in accordance with the intention to treat principle, ie, patients were analyzed by randomized groups regardless of treatment adherence or treatment actually received. A per-protocol analysis that excluded patients who took <70% of doses was performed as a sensitivity analysis.

The primary outcome of the number of COPD exacerbations was compared between groups using a generalized linear mixed model with the negative binomial distribution of the

outcome and a log-link function, with an appropriate over-dispersion parameter and length of time in the study as an offset.[30] Estimates were adjusted for baseline covariates associated with the outcome: center (random effect), recruitment setting, age, sex, smoking status, FEV_1, COPD exacerbations in the previous year, and baseline COPD treatments. Multiple imputation was not conducted because of negligible missing primary outcome data. For secondary outcomes, treatment groups were compared using appropriate methods: linear and generalized linear mixed models and mixed Cox regression models, all with adjustment for baseline covariates. TDI was additionally adjusted for BDI. There was no adjustment for multiple comparisons, and secondary analyses should be interpreted as hypothesis-generating. Analyses were performed using R Statistical Software version 4.2.1 (R Core Team, 2022; R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/). A 5% two-sided significance level was used; all estimates are presented with 95% confidence intervals.

Results

Patients

A total of 519 patients were randomized to bisoprolol vs placebo from October 17, 2018 to March 16, 2021, and from August 1, 2021 to May 31, 2022, after a 16-month interruption due to the COVID-19 pandemic. The trial was stopped in May 2022 because the funder could not support the study extension needed to enroll the additional planned number of patients. The final follow-up was on April 18, 2023. Of the 519 randomized patients, 261 were in the bisoprolol group and 258 were in the placebo group. After 4 post-randomization exclusions (2 bisoprolol, 2 placebo, Figure 1), 515 participants were eligible to initiate study medication: 259 bisoprolol, 256 placebo. Study recruitment occurred at 76 study sites (45 primary care,

31 secondary care), and 311 (60%) patients were enrolled from primary care clinics; 429 (83%) of all patients were enrolled prior to COVID-19. A total of 144 (28%) participants either did not initiate study drug treatment (4 bisoprolol, 4 placebo), or discontinued study medication (73 bisoprolol, 63 placebo) during the trial. Medication discontinuation occurred during study drug titration among 42 patients in the bisoprolol and 38 patients in the placebo group and after dose-titration in 31 patients in the bisoprolol group and 25 patients in the placebo group. Study medication cessation was similar between bisoprolol (28%) and placebo (25%) groups. After titration was completed, 71 (27%) patients received a fixed dose of 5mg bisoprolol daily, 37 (14%) received 3.75mg, 41 (16%) received 2.5mg and 62 (24%) received 1.25mg. For placebo, 110 (43%) received 4 tablets a day, 32 (13%) received 3 tablets, 43 (17%) received 2 tablets and 28 (11%) received 1 tablet a day (eTable 1).

Participant baseline characteristics were similar between bisoprolol and placebo groups (table 1). The mean (SD) age was 68 (7.9) years, 274 (53%) were male, and 160 (31%) currently smoked. COPD therapies were balanced between treatment groups, 380 (74%) were prescribed combined inhaled corticosteroid/long acting beta2 agonist/long-acting muscarinic antagonist (ICS/LABA/LAMA), 461(90%) were prescribed LAMAs in some form and 5% were using long term oxygen therapy.

Primary outcome

The primary outcome of patient-reported number of COPD exacerbations treated with oral corticosteroids and/or antibiotics during the 52-week treatment period was available for 514 (99.8%) of patients (259 bisoprolol, 255 placebo). There were 526 COPD exacerbations in the bisoprolol group, with a mean (SD) number of exacerbations of 2.03 (1.91) and 513 exacerbations in the placebo group, with mean (SD) number of exacerbations of 2.01 (1.75).

The unadjusted incidence rate ratio (IRR) (95% confidence interval), bisoprolol vs placebo, was 0.99 (0.84, 1.16), with adjusted IRR 0.97 (0.84, 1.13), p=0.72 (figure 2, eTable 2).

Secondary outcomes

This trial had 10 clinical secondary outcomes. The secondary outcome of median (IQR) time to first COPD exacerbation after randomization was 96.0 (27.0, 172.5) days for bisoprolol, and 70.0 (27.0, 160.0) days for placebo, adjusted hazard ratio [HR] (95% CI) 0.94 (0.78, 1.16), p=0.60 (figure 3).

As shown in figure 2 and eTable 2 there was no significant difference in hospitalizations for COPD exacerbations or in non-COPD related hospitalizations in the bisoprolol vs placebo groups. There were 24 deaths at 52-week follow-up, 11 (two COPD) in the bisoprolol group and 13 (nine COPD) in the placebo group. The HR (95% CI) for all-cause mortality in the bisoprolol group compared to placebo was 0.77 (0.34, 1.73), p=0.53, and the HR for COPD related mortality was 0.19 (0.04, 0.88), p=0.03 in the bisoprolol group vs placebo.

The mean difference (95% CI) in TDI quantified dyspnea at 52 weeks was -0.73 (-1.44, -0.01), p=0.05 (table 2), indicating an increase in dyspnea, however there was no difference in CAT scores at 52 weeks between the treatment groups. Table 2 and eTable 2 present the secondary outcomes of FEV_1, and MACE, but it is not possible to make meaningful comment because FEV_1 data were available for 51 patients at 52 weeks (because of COVID-19), and the MACE event rate was very low. HARQ data are not presented because very few centers administered the HARQ questionnaire.

Additional prespecified analyses

There was no evidence that the treatment effect significantly differed in any of the pre-specified subgroups (all interaction p>0.05): age, gender, smoking status, body mass index, baseline COPD treatments, exacerbation history, GOLD COPD classifications,[17] use of maintenance oral corticosteroids or bisoprolol dose (eFigure 2).

The follow-up of 334 participants included periods when COVID-19 shielding was advised, 90 completed treatment before COVID-19 and 90 were randomized after withdrawal of shielding advice. COVID-19 and shielding was associated with a 30% reduction in exacerbations, but there was no evidence that this affected the treatment effect (eTable 3).

The per-protocol analysis of the 357 (69.3%) patients (174 bisoprolol, 183 placebo) adherent with their study medication, i.e. took ≥70% of expected doses, is presented in eTables 4 & 5. For the primary outcome of COPD exacerbations treated with oral corticosteroids and/or antibiotics, the adjusted IRR was 1.05 (95% CI, 0.88, 1.27), p=0.58 for the bisoprolol vs placebo groups. The adjusted IRR was for COPD exacerbations needing hospitalization was 1.06 (0.62, 1.82), p=0.83.

Adverse Events

The number of patients with serious adverse events (SAEs) was similar between treatment groups (bisoprolol 37 [14.5%], placebo 36 [14.3%], relative risk RR [95% CI] 1.01 [0.62, 1.66], p=0.96) (eTable 6); bisoprolol was not associated with increased respiratory SAEs (bisoprolol 4, placebo 11), (eTable 7). The number of adverse reactions potentially related to bisoprolol also did not differ between bisoprolol (601) and placebo (632), (eTable 8) and bisoprolol was not associated with increased respiratory adverse reactions - bisoprolol 25 (9.8%), placebo 31 (12.3%) The most common reason for stopping study medication was an

organ class code “respiratory, thoracic and mediastinal disorders”, and was similar in the bisoprolol (12 (4.6%) and placebo 16 (6.3%) groups. (eTable 9).

Discussion

In this randomized clinical trial, among patients with COPD at risk of exacerbations, bisoprolol, compared with placebo, did not decrease the number of self-reported exacerbations treated with oral corticosteroids and/or antibiotics at 52 weeks of follow-up. There was no significant difference in 8 of the 10 clinical secondary outcomes. Bisoprolol was not significantly associated with clinical deterioration in COPD as quantified by exacerbations requiring hospital admission, and although bisoprolol was associated with reduced COPD-related mortality, the numbers were small and there was no reduction in all-cause mortality. Overall, the safety profile of bisoprolol was similar to placebo, with no increase in serious adverse events, or total or respiratory adverse reactions. In addition, patients were not more likely to discontinue bisoprolol for respiratory reasons.

Our conclusion that bisoprolol is not clinically beneficial in COPD is supported by the similarly sized (n=532) BLOCK-COPD trial in the United States.[15] BLOCK-COPD raised safety concerns because metoprolol was associated with a significant increase in COPD exacerbations requiring hospitalization, and the majority of deaths in the metoprolol group were attributed to COPD.[15] BLOCK-COPD also reported significant increases in breathlessness and CAT scores with use of metoprolol. In BICS, bisoprolol was not associated with an increase in COPD hospitalization or CAT score, and the majority of deaths in the bisoprolol group were not attributed to COPD. However, similar to BLOCK-COPD, BICS found that bisoprolol was associated with increased TDI-quantified breathlessness compared with placebo, although the effect was small and the 95% CI was wide (-1.44, -0.01).

The differences in outcomes between BICS and BLOCK-COPD may be due BLOCK-COPD patients having more severe COPD (mean FEV_1 40% vs 50% predicted, long term oxygen 40% vs 5%), less frequent use of concomitant LAMA (73% vs 90%), and greater cardiovascular co-morbidity (coronary artery disease 15% vs 4%, hypertension 46% vs 30%, diabetes 16% vs 11%). Also, the beta-blocker used in BLOCK-COPD (metoprolol) has a lower β_1:β_2 selectivity ratio compared to bisoprolol used in BICS.[15,31-33] The significance of concomitant LAMA therapy was illustrated by Jabbal et al who demonstrated that patients with COPD who had a mean baseline FEV_1 of 52% predicted had no significant worsening of lung function with the addition of bisoprolol 5mg while taking concomitant beclomethasone/formoterol or beclomethasone/formoterol with the LAMA tiotropium.[34]

The BICS trial has several strengths, including its study design as a randomized, double-blind placebo-controlled trial and its high follow-up rate. Additionally, 60% of patients were enrolled from primary care clinics and 40% were from secondary clinics, likely reflecting typical clinical practice across primary and secondary care sites in the UK. The high (74%) rate of triple (ICS/LABA/LAMA) inhaled therapy reflects best guideline-based practice in the UK primary care for the treatment of people with COPD at high risk of exacerbation. Primary COPD exacerbation outcome data were available for 99.8% of patients, likely due to the increased use of virtual (video or telephone) follow-up during the COVID-19 pandemic. To mitigate the issue of any potentially beneficial effect of bisoprolol being a consequence of treating ischaemic heart disease, BICS excluded patients with guideline recommended indications for beta-blocker treatment and patients stopped study treatment if such indications arose during the treatment period.

Limitations

This study has several limitations. First, due to the COVID-19 pandemic and subsequent loss of funding, this study enrolled only 519 patients, which represented 33% of the target enrollment of 1574 patients. Second, 28% of patients discontinued their study drug. While this was the same rate as in the TWICS trial, it was higher than the 8.7% reported by BLOCK-COPD.[15,29] Third, race and ethnicity data were not reported in this study. Fourth, only 27% of patients in the bisoprolol group received the fixed dose of 5mg daily, and 18% could not tolerate bisoprolol during titration. Fifth, 31% of study participants took <70% of expected doses, although adherence did not differ between the bisoprolol and placebo groups. Sixth, it is possible that patients in the bisoprolol group were unblinded by medication-induced reductions in blood pressure and heart rate. However, based data from studies of bisoprolol in heart failure,[35] research staff and patients were informed that it was not possible to reliably establish treatment allocation from study medication effects on heart rate, and blood pressure.

Conclusion

Among people with COPD at high risk of exacerbation, treatment with bisoprolol did not reduce the number of self-reported COPD exacerbations requiring treatment with oral corticosteroids and/or antibiotics.

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Conflicts of interest

Prof Lee, Dr McMeekin and Dr Short report no conflicts of interest.

Ms Campbell, Dr Cotton, Prof Devereux, Dr Fielding, Dr Gompertz, Prof MacLennon, Dr Nath and Prof Wu report NIHR funding to their institutions during the course of the study.

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membership; Consultancy agreements; Lectures/speaking engagements - Fees paid to Observational and Pragmatic Research Institute., personal fees from Teva Pharmaceuticals Consultancy agreements; Lectures/speaking engagements; Payment for travel/accommodation/meeting expenses - fees paid to Observational and Pragmatic Research Institute., grants from Novartis Grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute). Board membership; Consultancy agreements; Lectures/speaking engagements; Payment for travel/accommodation/meeting expenses; Fees paid to Observational and Pragmatic Research Institute., personal fees from Novartis Grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute). Board membership; Consultancy agreements; Lectures/speaking engagements; Payment for travel/accommodation/meeting expenses; Fees paid to Observational and Pragmatic Research Institute., grants from Regeneron Pharmaceuticals Board membership; Grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd); Lectures/speaking engagements - Fees paid to Observational and Pragmatic Research Institute., personal fees from Regeneron Pharmaceuticals Board membership; Grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd); Lectures/speaking engagements - Fees paid to Observational and Pragmatic Research Institute., grants from Sanofi Genzyme Board membership; Grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd); Lectures/speaking engagements - Fees paid to Observational and Pragmatic Research Institute., personal fees from Sanofi Genzyme Board membership; Grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd); Lectures/speaking engagements - Fees paid to

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Access to Data and Data Analysis

Graham Devereux (Co chief investigator) and Prof Amanda Lee (Study statistician) had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Dr Mintu Nath (University of Aberdeen), Dr Nicola McMeekin (University of Glasgow) and Prof Amanda Lee (University of Aberdeen) conducted and are responsible for the data analysis.

Data Sharing

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.

Disclaimer

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Figure legends

Figure 1: Diagram illustrating enrolment, randomisation and follow up of participants.

Abbreviations

IC inclusion criteria

BP blood pressure

m months

Figure 2: Primary and secondary outcomes expressed as adjusted incidence rate ratios (IRR) or hazard ratios (HR) and corresponding 95% confidence intervals

Footnote

Estimates of IRR and HR and corresponding 95% confidence intervals were obtained from models adjusted for: centre (as a random effect), recruitment setting (primary or secondary care), age centred on the mean, sex, smoking status (current vs ex), FEV_1 % predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long term antibiotics.

Abbreviation
PY person year

Figure 3: Kaplan–Meier plot of freedom from exacerbation of COPD in the two trial groups.

Footnote

Legend includes median (IQR) time in days to first exacerbation for bisoprolol and placebo groups.

672 TABLE 1: Baseline characteristics of participants

	Bisoprolol N=259	Placebo N=256
Age (years), mean (SD)	67.7 (8.0)	67.7 (7.7)
Male, n (%)	134 (51.7)	140 (54.7)
Female n (%)	125 (48.3)	116 (45.3)
Body mass index kg/m^2 (mean, SD)	26.4 (5.7) [N=258]	27.2 (6.6) [N=254]
Currently smokes, n (%)	78 (30.1)	82 (32.0)
Pack years smoking (mean, SD)	45.1 (24.4)	45.2 (26.0) [N=255]
Exacerbations[a] in the last 12 months, (mean, SD)	3.5 (1.8)	3.6 (2.1)
Exacerbations with hospitalisation in last 12 months, (mean, SD)	0.4 (0.8)	0.5 (1.1)
COPD therapies		
Combination ICS, LABA, LAMA, n (%)	192 (74.1)	188 (73.4)
Combination ICS, LABA, n (%)	22 (8.5)	13 (5.1)
Combination LABA, LAMA, n (%)	26 (10.0)	31 (12.1)
Single LABA, n (%)	1 (0.4)	1 (0.4)
Single LAMA, n (%)	9 (3.5)	14 (5.5)
Long-term oxygen, n (%)	16 (6.2)	9 (3.5)
Long term azithromycin, n (%)	30 (11.6)	33 (12.9)
FEV_1 % predicted, (mean, SD)	49.2 (19.0) [N=258]	51.1 (19.1)
FEV_1/FVC, % ratio, median (IQR)	44.6 (36.4, 59.2) [N=256]	46.2 (36.6, 58.6) [N=253]
Baseline dyspnea index[b], (mean, SD)	6.6 (2.8) [N=252]	6.6 (2.7) [N=244]
COPD assessment test[c], (mean, SD)	22.7 (8.1)	22.0 (8.0)
Resting heart rate (/min), mean (SD)	82.2 (11.8)	80.3 (12.4)
Systolic blood pressure, (mmHg), mean (SD)	137.0 (18.9)	135.8 (17.7)
Diastolic blood pressure, (mmHg) mean (SD)	79.9 (10.7)	79.6 (9.5)

Hypertension, n (%)	73 (28.2)	79 (30.9)
Anxiety/depression treated in last 5 years, n (%)	71 (27.4)	77 (30.1)
Osteoporosis, n (%)	34 (13.1)	37 (14.5)
Asthma diagnosis after age 40 years, n (%)	28 (10.8)	35 (13.7)
Diabetes Mellitus, n (%)	22 (8.5)	33 (12.9)
Bronchiectasis, n (%)	17 (6.6)	18 (7.0)
Cerebrovascular event, n (%)	13 (5.0)	17 (6.6)
Ischemic Heart Disease, n (%)	11 (4.2)	11 (4.3)

673

674 [a]Exacerbation defined as symptomatic deterioration in COPD requiring treatment with oral
675 corticosteroids and/or antibiotics

676 [b]Baseline dyspnea index (BDI): scale 0-12, lower scores indicative of worse breathlessness

677 [c]COPD Assessment Test (CAT): scale 0-40, higher scores indicative of greater impact of COPD on
678 health and wellbeing, MCID 2 units. A score of 20-30 is indicates that COPD is having a high impact
679 on health and wellbeing

680

681 Abbreviations

682 ICS inhaled corticosteroid

683 LAMA long acting muscarinic antagonists

684 LABA, long acting beta2 agonist

685 MCID Minimal clinically important difference

686 N number of patients

687 n number of patients with the characteristic

688 SD Standard Deviation

689

690

TABLE 2: Secondary outcomes for participants allocated to bisoprolol and placebo.

	FEV_1% predicted (secondary outcome)			CAT score[c] (secondary outcome)			TDI[d] (secondary outcome)		
	Bisoprolol	Placebo	Adjusted[a] mean difference (95% CI)	Bisoprolol	Placebo	Adjusted[a] mean difference (95% CI)	Bisoprolol	Placebo	Adjusted[b] mean difference (95% CI)
Baseline									
Mean	49.3%	51.3%		22.7	22.0				
(SD)	(19.0)	(19.1)		(8.12)	(8.04)				
N	256	251		259	255				
26 weeks									
Mean	47.8%	47.0%	-0.75	20.3	18.7	1.64	199	198	-0.62
(SD)	(18.8)	(19.3)	(-3.61, 2.10)	(8.85)	(9.25)	(0.05, 3.23)	-0.83	-0.34	(-1.16, -0.07)
N	92	87	p=0.61	219	222	p=0.04	(2.78)	(2.91)	p=0.03
52 weeks									
Mean	43.3%	53.1%	-4.53	19.4	19.8	-0.59	183	188	-0.73
(SD)	(20.8)	(18.9)	(-10.2, 1.16)	(8.86)	(9.40)	(-2.26, 1.07)	-1.73	-1.01	(-1.44, -0.01)
N	30	21	p=0.13	207	202	p=0.48	(3.66)	(3.58)	p=0.05

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

[b]adjusted for: centre (as a random effect), recruitment setting (primary or secondary care), age centred on the mean, sex, smoking status (current vs ex), FEV_1 % predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long term antibiotics and baseline dyspnea index.

Mean Difference represents Overall Mean Difference between Bisoprolol and Placebo

[c]COPD Assessment Test (CAT): scale 0-40, higher scores indicative of greater impact of COPD on health and wellbeing, MCID 2 units

[d]TDI Transition dyspnea index: scale -9 to +9, lower scores indicative of worse breathlessness, MCID 1 unit

Abbreviations

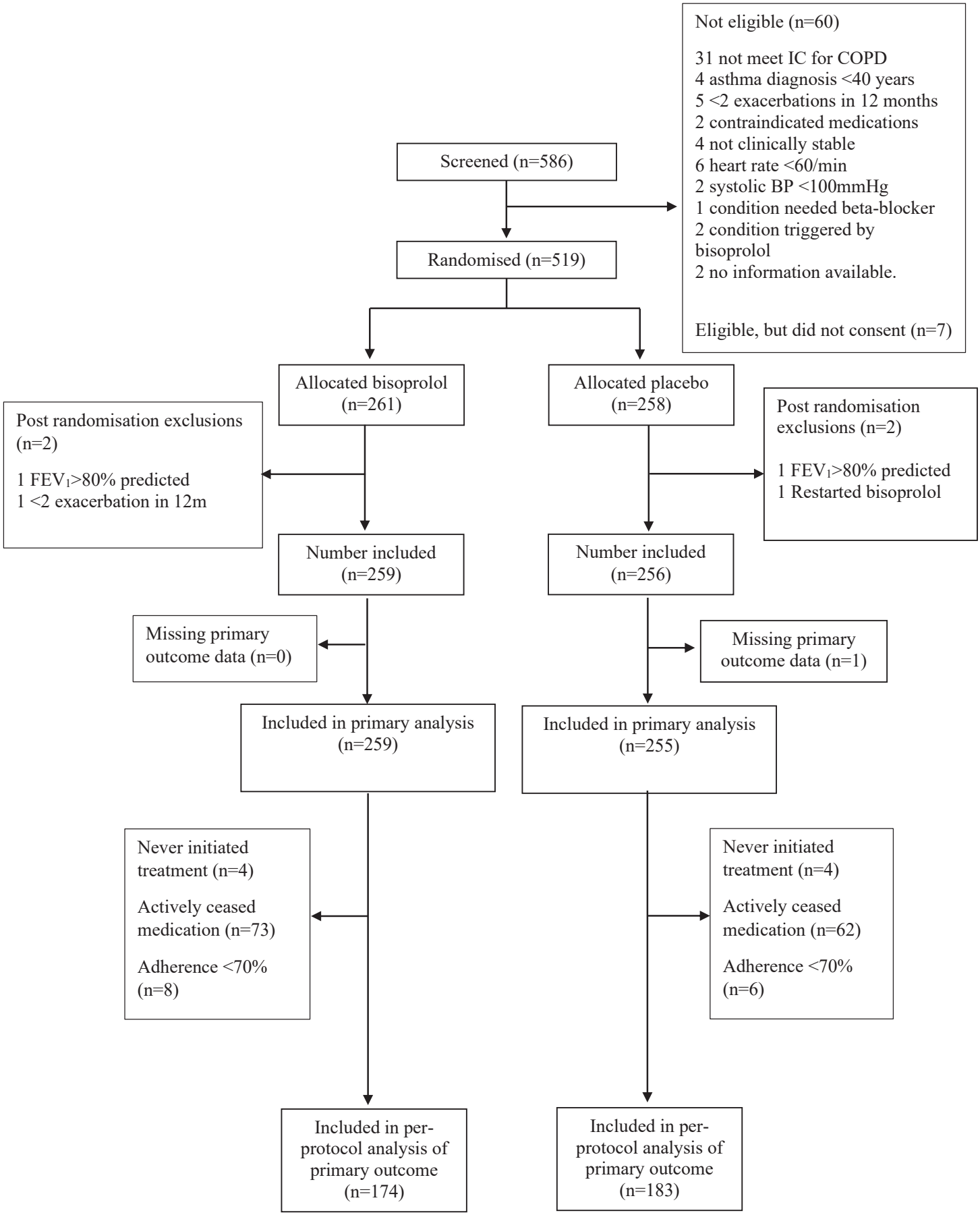
CI confidence interval,

MCID minimal clinically important difference

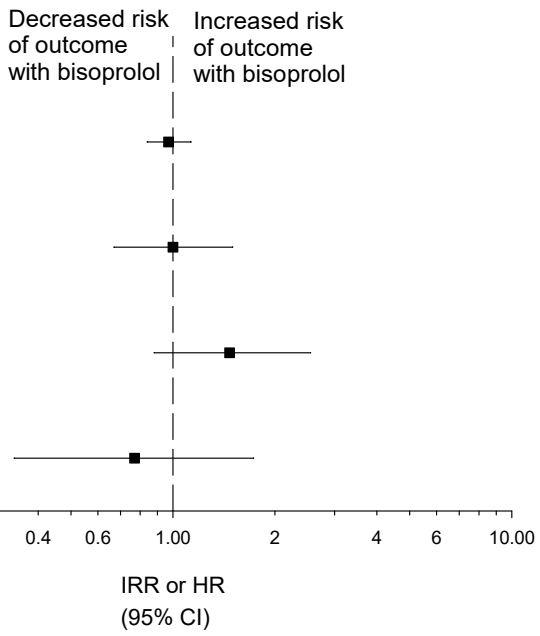
N number of patients

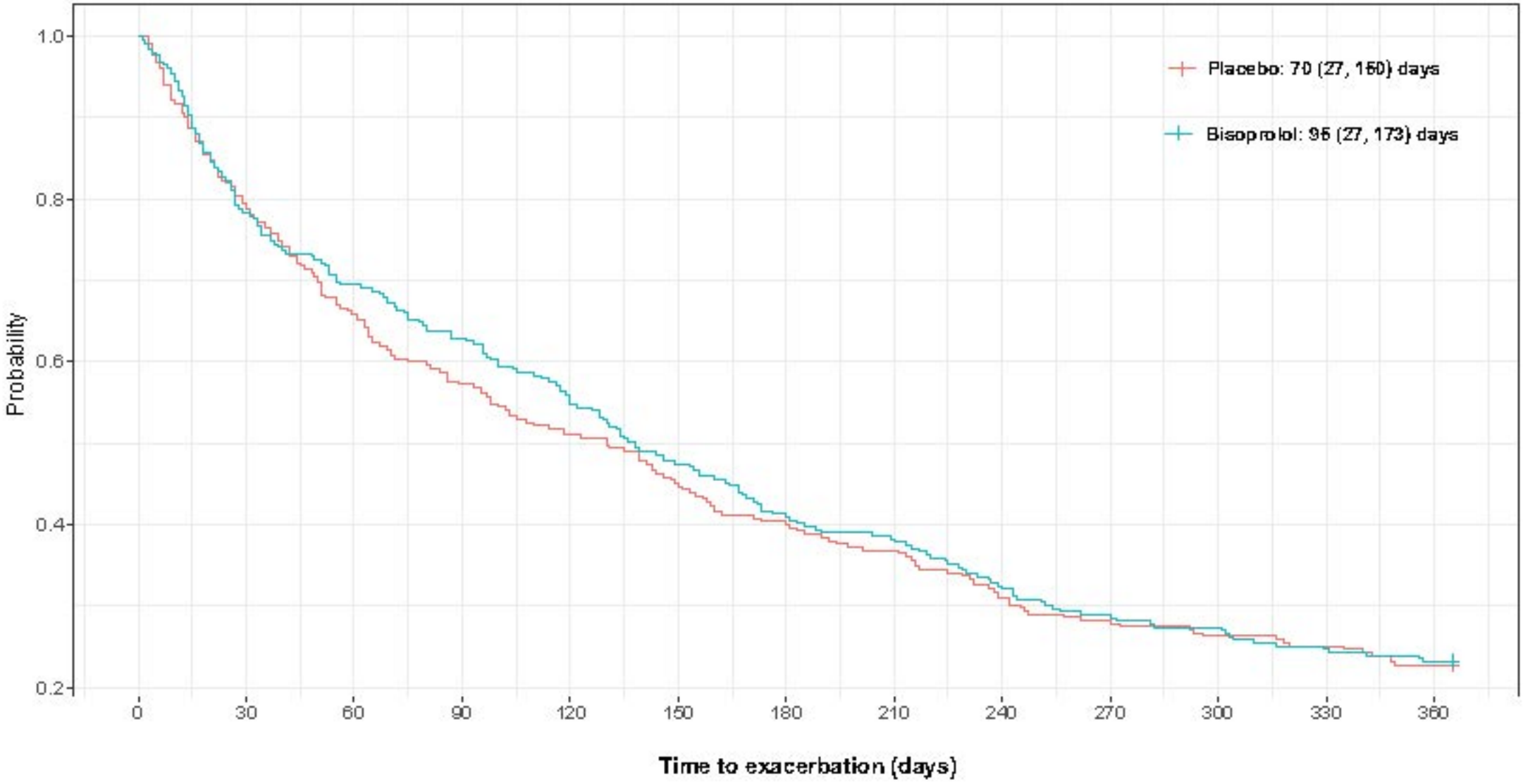
SD standard deviation

706

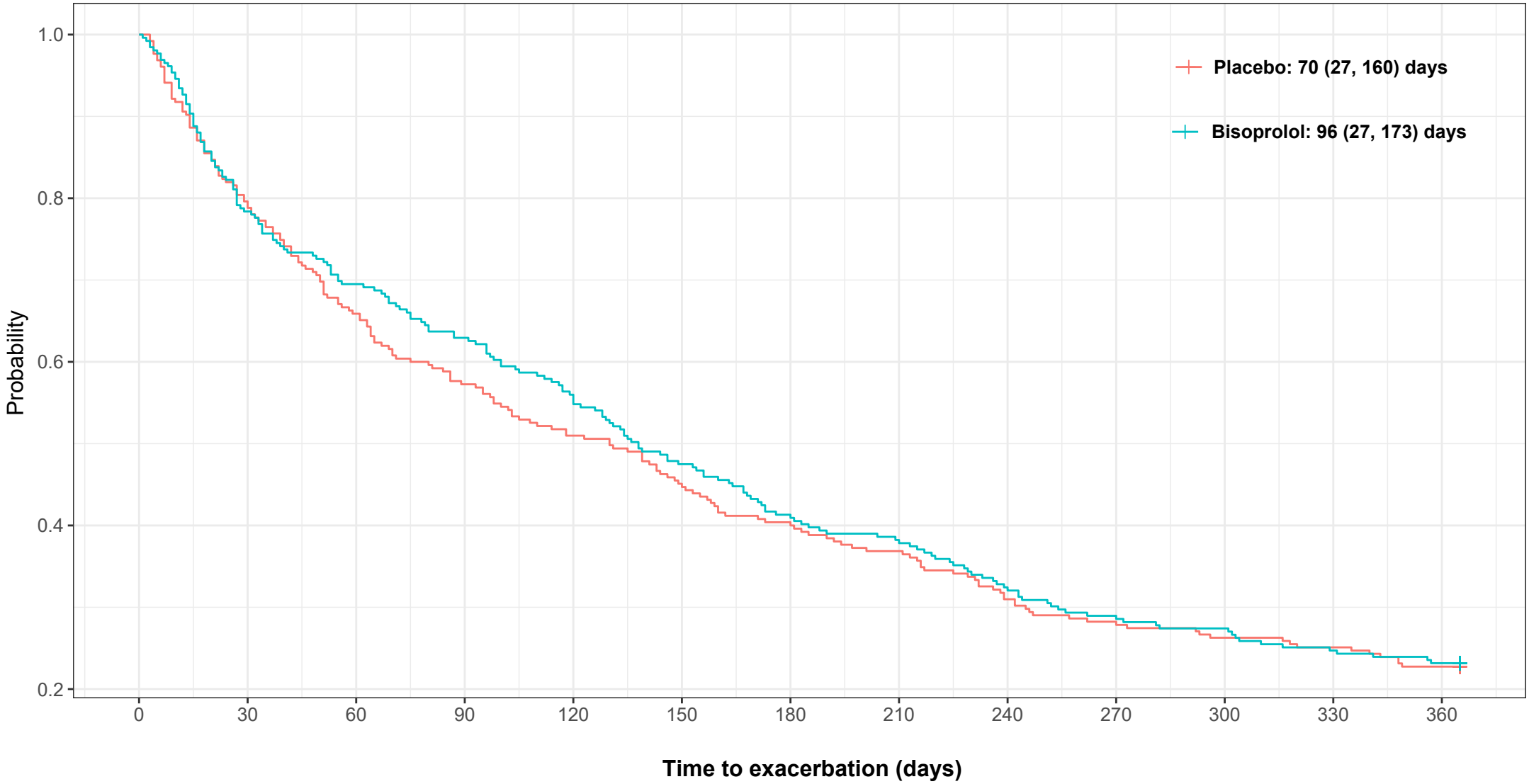

Not eligible (n=60)
31 not meet IC for COPD
4 asthma diagnosis <40 years
5 <2 exacerbations in 12 months
2 contraindicated medications
4 not clinically stable
6 heart rate <60/min
2 systolic BP <100mmHg
1 condition needed beta-blocker
2 condition triggered by bisoprolol
2 no information available.
Eligible, but did not consent (n=7)
Screened (n=586)
Randomised (n=519)
Allocated bisoprolol (n=261)
Allocated placebo (n=258)
Post randomisation exclusions (n=2)
1 FEV1>80% predicted
1 <2 exacerbation in 12m
Post randomisation exclusions (n=2)
1 FEV1>80% predicted
1 Restarted bisoprolol
Number included (n=259)
Number included (n=256)
Missing primary outcome data (n=0)
Missing primary outcome data (n=1)
Included in primary analysis (n=259)
Included in primary analysis (n=255)
Never initiated treatment (n=4)
Actively ceased medication (n=73)
Adherence <70% (n=8)
Never initiated treatment (n=4)
Actively ceased medication (n=62)
Adherence <70% (n=6)
Included in per-protocol analysis of primary outcome (n=174)
Included in per-protocol analysis of primary outcome (n=183)

	Number of events		Adj IRR or HR (95% CI)[a]
	Bisoprolol PY=257	Placebo PY=248	
Primary outcome			
COPD exacerbations (IRR)	526	513	0.97 (0.84 to 1.13)
Secondary outcomes			
COPD hospital admissions (IRR)	71	68	1.00 (0.67 to 1.50)
Non-COPD hospital admissions (IRR)	47	32	1.47 (0.88 to 2.55)
All-cause mortality (HR)	11	13	0.77 (0.34 to 1.73)





Placebo													
At Risk	255	203	168	146	130	115	103	94	79	72	67	64	58
Events	0	54	87	109	125	141	153	161	176	184	188	191	197
Bisoprolol													
At Risk	259	203	180	163	145	123	107	99	84	75	71	64	60
Events	0	56	79	96	117	136	153	161	176	185	188	195	199



Placebo													
At Risk	255	203	168	146	130	115	103	94	79	72	67	64	58
Events	0	54	87	109	125	141	153	161	176	184	188	191	197
Bisoprolol													
At Risk	259	203	180	163	145	123	107	99	84	75	71	64	60
Events	0	56	79	96	117	136	153	161	176	185	188	195	199