JAMA | Original Investigation

Bisoprolol in Patients With Chronic Obstructive Pulmonary Disease at High Risk of Exacerbation
The BICS Randomized Clinical Trial

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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 (ratio of forced expiratory volume in the first second of expiration [FEV_1] to forced vital capacity <0.7; FEV_1 <80% predicted) and at least 2 COPD exacerbations treated with oral corticosteroids, antibiotics, or both 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 during 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, antibiotics, or both during 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 postrandomization. Among the 515 patients (mean [SD] age, 68 [7.9] years; 274 men [53%]; mean FEV_1, 50.1%), primary outcome data were available for 514 patients (99.8%) and 371 (72.0%) continued taking the study drug. The primary outcome of patient-reported COPD exacerbations treated with oral corticosteroids, antibiotics, or both was 526 in the bisoprolol group, with a mean exacerbation rate of 2.03/y, vs 513 exacerbations in the placebo group, with a mean exacerbation rate of 2.01/y. The adjusted incidence rate ratio was 0.97 (95% CI, 0.84-1.13; *P* = .72). Serious adverse events occurred in 37 of 255 patients in the bisoprolol group (14.5%) vs 36 of 251 in the placebo group (14.3%; relative risk, 1.01; 95% CI, 0.62-1.66; *P* = .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, antibiotics, or both.

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Visual Abstract

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Chronic obstructive pulmonary disease (COPD) is the world's third leading cause of death and sixth leading cause of disability.[1,2] Exacerbations of COPD are associated with reduced quality of life, increased mortality, and lost productivity and are key drivers of health care 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]

β-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 β-blockers used for cardiovascular indications have shown that β_1-selective β-blockers are well tolerated in patients with COPD and their use has been associated with reductions in exacerbations and mortality.[9-14] However, the β-Blockers for the Prevention of Acute Exacerbations of Chronic Obstructive Pulmonary Disease (BLOCK 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 2-fold increased risk of exacerbation requiring hospitalization. Although metoprolol was not associated with a significant increase in mortality, most 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 β-blocker bisoprolol to treatment of people with COPD at high risk of exacerbation reduced the rate of moderate to severe COPD exacerbations.

Key Points

Question For people with chronic obstructive pulmonary disease (COPD) at high risk of exacerbations, does bisoprolol reduce the number of exacerbations?

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

Meaning Treatment with bisoprolol did not reduce COPD exacerbations requiring treatment with oral corticosteroids, antibiotics, or both.

Methods

Trial Design and Oversight

This study was a double-blind, placebo-controlled, randomized, multicenter clinical trial comparing the addition of bisoprolol or placebo with 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 Supplement 4. See Supplement 3 for a summary of protocol amendments.

The trial was approved by Scotland A Research Ethics Committee and the Medicines and Healthcare products Regulatory Agency. All patients provided written informed consent. This study followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Study Population

Patients were recruited from 76 UK sites (45 primary care clinics and 31 secondary care clinics). In primary care, patients were identified from electronic patient records and community COPD services records. In secondary care, patients were identified from inpatient and outpatient records. Patients were eligible if they were aged 40 years or older with COPD and had at least moderate airflow obstruction (ratio of forced expiratory volume in the first second of expiration [FEV_1] to forced vital capacity <0.7; FEV_1 <80% predicted),[17] smoking history greater than 10 pack-years, and at least 2 exacerbations treated with oral corticosteroids, antibiotics, or both in the previous year. Exclusion criteria included a diagnosis of asthma before age 40 years; resting heart rate less than 60/min; systolic blood pressure less than 100 mm Hg; interacting drugs such as calcium-channel blockers, class I antiarrhythmic drugs, and centrally acting antihypertensive medications (eg, clonidine); or conditions for which β-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 in Supplement 2.[16]

Study Design

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

Treatment Protocol

Patients were treated with bisoprolol (using 1.25-mg tablets) or visually identical placebo tablets, both manufactured by Tiofarma B.V., for 52 weeks. Study drug was started at 1.25 mg once daily and up-titrated as tolerated during 4 titration assessments during approximately 7 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 according to intolerable adverse effects (eg, fatigue), heart rate, systolic blood pressure, and FEV_1 (eFigure 1 in Supplement 1). After titration was completed, patients continued a fixed dose of once-daily bisoprolol at 1.25, 2.50, 3.75, or 5 mg; or placebo equivalent for the remainder of the 52-week treatment period, after which the study medication was titrated.

Outcomes

The primary outcome was patient-reported number of COPD exacerbations treated with oral corticosteroids, antibiotics, or both during the 52-week treatment period.[20] To be considered as separate events, exacerbations had to be spaced by

at least 2 weeks.[20] Outcome data were collected at baseline and at 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, scale 0-40, with higher scores indicative of greater effect of COPD on health and well-being; minimal clinically important difference, 2 units)[21]; breathlessness assessed with the Baseline Dyspnea Index (scale 0-12, with lower scores indicative of worse breathlessness) and subsequent changes by the Transition Dyspnea Index (scale −9 to 9, with lower scores indicative of greater deterioration in breathlessness; minimal clinically important difference, 1 unit)[22,23]; postbronchodilator spirometry conducted according to American Thoracic Society/European Respiratory Society guidelines (FEV_1; forced vital capacity as percentage predicted)[24]; number of major adverse cardiovascular events[25]; COPD-related mortality; all-cause mortality; and in self-selected centers, the Hull Airway Reflux Questionnaire score, which was used to assess symptoms not elucidated by the COPD Assessment Test or dyspnea indices.[26]

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

Pandemic Procedures

COVID-19 resulted in a 16-month suspension of recruitment (March 16, 2020, to July 31, 2021). In the United Kingdom 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 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 whether patients met study inclusion criteria. For dose titration of bisoprolol, patient report of worsening breathlessness replaced measurement of 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, patients 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 at least 2 self-reported exacerbations in a year, the mean (SD) number of COPD exacerbations in the following year was 2.22 (1.86).[28] Assuming a similar rate in the placebo group, 669 patients were needed in each trial group to detect a 15% reduction in exacerbations (ie, from 2.22 to 1.89) with 90% power at the 2-sided 5% α level. Allowing for 15% withdrawal from study treatment, 787 patients were required in each treatment group (ie, 1574 in total). The proposed treatment effect of a 15% reduction in exacerbations was based on 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 less than 70% of doses was performed as a sensitivity analysis.

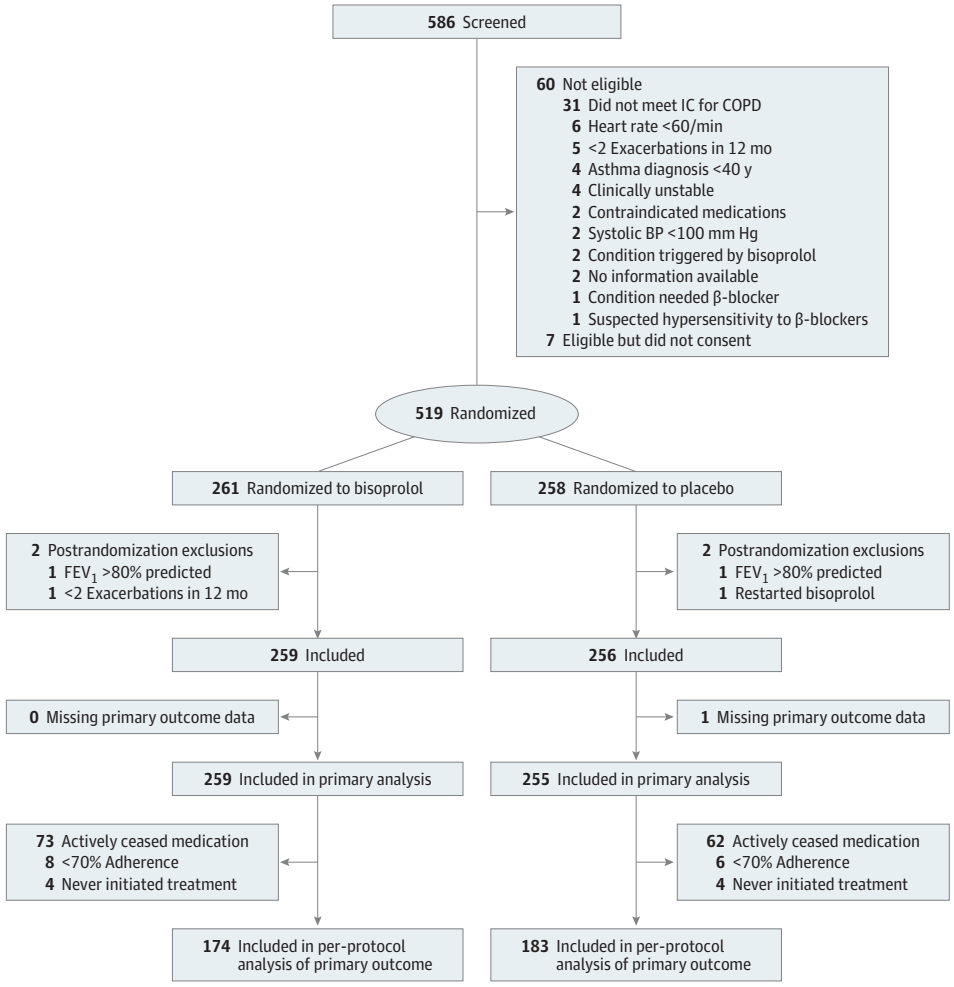
The primary outcome of the number of COPD exacerbations was compared between groups by using a generalized linear mixed model with the negative binomial distribution of the outcome and a log-link function, with an appropriate overdispersion parameter and length of time in the study as an offset.[30] 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 by using appropriate methods: linear and generalized linear mixed models and mixed Cox regression models, all with adjustment for baseline covariates. The Transition Dyspnea Index score was additionally adjusted for the Baseline Dyspnea Index score. There was no adjustment for multiple comparisons, and secondary analyses should be interpreted as hypothesis generating. Analyses were performed with R version 4.2.1 (R Foundation for Statistical Computing). A 5% 2-sided significance level was used; all estimates are presented with 95% CIs.

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 randomly assigned patients, 261 were in the bisoprolol group and 258 were in the placebo group. After 4 postrandomization exclusions (2 bisoprolol, 2 placebo) (**Figure 1**), 515 patients 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 patients (60%) were enrolled from primary care clinics; 429 patients (83%) of the 519 randomly assigned patients were enrolled before the COVID-19 pandemic. A total of 144 patients (28%) either did not initiate study drug treatment (4 bisoprolol, 4 placebo) or discontinued study medication (73 bisoprolol, 62 placebo) during the trial, with 371 (72.0%) continuing to take the study drug. Medication discontinuation occurred during

Figure 1. Enrollment, Randomization, and Follow-Up of Patients



BP indicates blood pressure; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in the first second of expiration; and IC, inclusion criteria.

study drug titration among 42 patients in the bisoprolol group and 38 patients in the placebo group and after dose titration for 31 patients in the bisoprolol group and 25 patients in the placebo group. Study medication cessation was similar between the bisoprolol group (73 of 259 [28%]) and placebo group (63 of 256 [25%]). After titration was completed, 71 of 259 patients (27%) received a fixed dose of 5 mg bisoprolol daily, 37 (14%) received 3.75 mg, 41 (16%) received 2.5 mg, and 62 (24%) received 1.25 mg. For placebo, 110 of 256 patients (43%) received 4 tablets daily, 32 (13%) received 3 tablets daily, 43 (17%) received 2 tablets daily, and 28 (11%) received 1 tablet daily (eTable 1 in Supplement 1).

Patient baseline characteristics were similar between bisoprolol and placebo groups (**Table 1**). The mean (SD) age was 68 (7.9) years, 274 of the 515 patients were male (53%), 241 were female (47%), mean (SD) FEV_1 was 50.1% (19.1%), and 160 currently smoked (31%). The COPD therapies were balanced between treatment groups: 380 patients (74%) were prescribed combined inhaled corticosteroid/long-acting β_2-agonist/long-acting muscarinic antagonist, 461 patients (90%) were prescribed long-acting muscarinic antagonists in some form, and 25 patients (5%) were prescribed long-term oxygen therapy.

Primary Outcome

The primary outcome of patient-reported number of COPD exacerbations treated with oral corticosteroids, antibiotics, or both during the 52-week treatment period was available for 514 patients (99.8%; 259 bisoprolol, 255 placebo). There were 526 COPD exacerbations in the bisoprolol group, with a mean (SD) number of exacerbations of 2.03/y (1.91/y), and 513 exacerbations in the placebo group, with a mean (SD) number of exacerbations of 2.01/y (1.75/y). The unadjusted incidence rate ratio for bisoprolol vs placebo was 0.99 (95% CI, 0.84-1.16), with an adjusted incidence rate ratio of 0.97 (95% CI, 0.84-1.13; $P = .72$) (**Figure 2**; eTable 2 in Supplement 1).

Secondary Outcomes

This trial had 10 clinical secondary outcomes. The secondary outcome of median time to first COPD exacerbation after randomization was 96.0 days (IQR, 27.0-172.5 days) for bisoprolol

Table 1. Baseline Characteristics of Patients

	No. (%)	
	Bisoprolol (n = 259)	Placebo (n = 256)
Age, mean (SD), y	67.7 (8.0)	67.7 (7.7)
Male, No. (%)	134 (51.7)	140 (54.7)
Female, No. (%)	125 (48.3)	116 (45.3)
Body mass index, mean (SD) [No.]	26.4 (5.7) [258]	27.2 (6.6) [254]
Currently smokes, No. (%)	78 (30.1)	82 (32.0)
Pack-years smoking, mean (SD) [No.]	45.1 (24.4) [259]	45.2 (26.0) [255]
Exacerbations in last 12 mo, mean (SD)[a]	3.5 (1.8)	3.6 (2.1)
Exacerbations with hospitalization in last 12 mo, mean (SD)	0.4 (0.8)	0.5 (1.1)
COPD therapies		
Combination ICS, LABA, and LAMA, No. (%)	192 (74.1)	188 (73.4)
Combination ICS and LABA, No. (%)	22 (8.5)	13 (5.1)
Combination LABA and LAMA, No. (%)	26 (10.0)	31 (12.1)
Single LABA, No. (%)	1 (0.4)	1 (0.4)
Single LAMA, No. (%)	9 (3.5)	14 (5.5)
Long-term oxygen, No. (%)	16 (6.2)	9 (3.5)
Long-term azithromycin, No. (%)	30 (11.6)	33 (12.9)
FEV_1 % predicted, mean (SD) [No.]	49.2 (19.0) [258]	51.1 (19.1) [256]
FEV_1/FVC, % ratio, median (IQR) [No.]	44.6 (36.4-59.2) [256]	46.2 (36.6-58.6) [253]
Baseline dyspnea index, mean (SD) [No.][b]	6.6 (2.8) [252]	6.6 (2.7) [244]
COPD assessment test, mean (SD)[c]	22.7 (8.1)	22.0 (8.0)
Resting heart rate, mean (SD), /min	82.2 (11.8)	80.3 (12.4)
Systolic blood pressure, mean (SD), mm Hg	137.0 (18.9)	135.8 (17.7)
Diastolic blood pressure, mean (SD), mm Hg	79.9 (10.7)	79.6 (9.5)
Hypertension, No. (%)	73 (28.2)	79 (30.9)
Anxiety or depression treated in last 5 y, No. (%)	71 (27.4)	77 (30.1)
Osteoporosis, No. (%)	34 (13.1)	37 (14.5)
Asthma diagnosis after age 40 y, No. (%)	28 (10.8)	35 (13.7)
Diabetes, No. (%)	22 (8.5)	33 (12.9)
Bronchiectasis, No. (%)	17 (6.6)	18 (7.0)
Cerebrovascular event, No. (%)	13 (5.0)	17 (6.6)
Ischemic heart disease, No. (%)	11 (4.2)	11 (4.3)

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonists; MCID, minimal clinically important difference. Body mass index is calculated as weight in kilograms divided by height in meters squared.

[a] Exacerbation defined as symptomatic deterioration in COPD requiring treatment with oral corticosteroids, antibiotics, or both.

[b] Baseline Dyspnea Index: scale 0 to 12, with lower scores indicative of worse breathlessness.

[c] COPD Assessment Test: scale 0 to 40, with higher scores indicative of greater effect of COPD on health and well-being; MCID = 2 units. A score of 20 to 30 indicates that COPD is having a "high impact" on health and well-being.

and 70.0 days (IQR, 27.0-160.0 days) for placebo (adjusted hazard ratio, 0.94; 95% CI, 0.78-1.16; P = .60) (**Figure 3**).

As shown in Figure 2 and eTable 2 in Supplement 1, 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 (2 COPD) in the bisoprolol group and 13 (9 COPD) in the placebo group. The hazard ratio for all-cause mortality in the bisoprolol group compared with the placebo group was 0.77 (95% CI, 0.34-1.73; P = .53), and the hazard ratio for COPD-related mortality was 0.19 (95% CI, 0.04-0.88; P = .03) in the bisoprolol group vs placebo group.

The mean difference in the Transition Dyspnea Index score–quantified dyspnea at 52 weeks was −0.73 (95% CI, −1.44 to −0.01; P = .05) (**Table 2**), indicating an increase in dyspnea; however, there was no difference in COPD Assessment Test scores at 52 weeks between the treatment groups. Table 2 and eTable 2 in Supplement 1 present the secondary outcomes of FEV_1 and major adverse cardiovascular events, 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 major adverse cardiovascular events event rate was very low. Hull Airway Reflux Questionnaire data are not presented because few centers administered the questionnaire.

Additional Prespecified Analyses

There was no evidence that the treatment effect significantly differed in any of the prespecified subgroups (all interaction P > .05): age, sex, smoking status, body mass index (calculated as weight in kilograms divided by height in meters squared), baseline COPD treatments, exacerbation history, Global Initiative for Chronic Obstructive Lung Disease COPD classifications,[17] use of maintenance oral corticosteroids, or bisoprolol dose (eFigure 2 in Supplement 1).

The follow-up of 334 patients included periods when COVID-19 shielding was advised; 90 patients completed treatment before the COVID-19 pandemic and 90 patients 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 in Supplement 1).

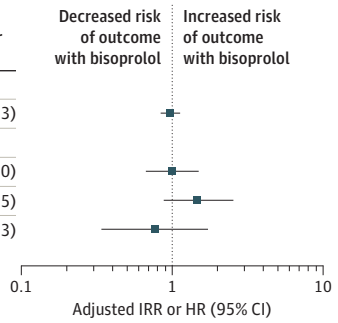
The per-protocol analysis of the 357 patients (174 bisoprolol, 183 placebo [69.3%]) adherent with their study medication (ie, took ≥70% of expected doses) is presented in eTables 4 and 5 in Supplement 1. For the primary outcome of COPD exacerbations treated with oral corticosteroids, antibiotics, or both, the adjusted incidence rate ratio was 1.05 (95% CI, 0.88-1.27; P = .58) for the bisoprolol vs placebo groups. The adjusted incidence rate ratio for COPD exacerbations needing hospitalization was 1.06 (95% CI, 0.62-1.82; P = .83).

Adverse Events

The number of patients with serious adverse events was similar between treatment groups (bisoprolol, 37 of 255 [14.5%]; placebo, 36 of 251 [14.3%]; relative risk, 1.01; 95% CI, 0.62-1.66; P = .96) (eTable 6 in Supplement 1); bisoprolol was not associated with increased respiratory serious adverse events (bisoprolol, 4; placebo, 11) (eTable 7 in Supplement 1). The number of adverse reactions potentially related to bisoprolol also did not differ between bisoprolol (601) and placebo (632) (eTable 8 in Supplement 1), and bisoprolol was not associated with increased respiratory adverse reactions (bisoprolol, 25 of

Figure 2. Primary and Secondary Outcomes Expressed as Adjusted Incidence Rate Ratios (IRRs) or Hazard Ratios (HRs)

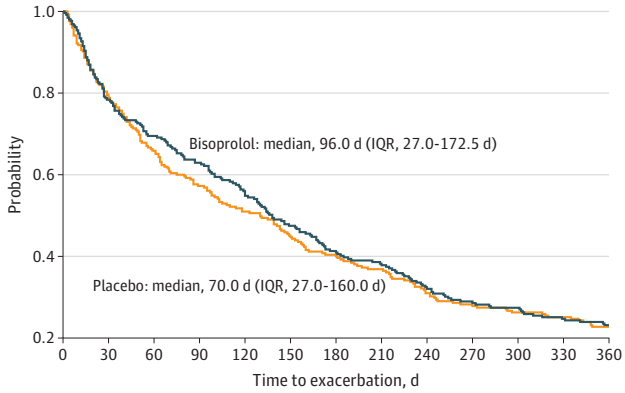
	No. of events		
	Bisoprolol (PY = 257)	Placebo (PY = 248)	Adjusted IRR or HR (95% CI)
Primary outcome			
COPD exacerbations (IRR)	526	513	0.97 (0.84-1.13)
Secondary outcomes			
COPD hospital admissions (IRR)	71	68	1.00 (0.67-1.50)
Non-COPD hospital admissions (IRR)	47	32	1.47 (0.88-2.55)
All-cause mortality (HR)	11	13	0.77 (0.34-1.73)



Estimates of IRR and HR and corresponding 95% CIs were obtained from models adjusted for center (as a random effect), recruitment setting (primary or secondary care), age centered on the mean, sex, smoking status (current vs former), forced expiratory volume in the first second of expiration percentage predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, and treatment with long-term antibiotics.

COPD indicates chronic obstructive pulmonary disease; PY, person-years.

Figure 3. Freedom From Exacerbation of Chronic Obstructive Pulmonary Disease in the 2 Trial Groups



Placebo													
No. at risk	255	203	168	146	130	115	103	94	79	72	67	64	58
No. of events	0	54	87	109	125	141	153	161	176	184	188	191	197
Bisoprolol													
No. at risk	259	203	180	163	145	123	107	99	84	75	71	64	60
No. of events	0	56	79	96	117	136	153	161	176	185	188	195	199

The curves include median time to first exacerbation for the bisoprolol and placebo groups.

255 [9.8%]; placebo, 31 of 251 [12.3%]). The most common reason for stopping study medication was an organ class code "respiratory, thoracic and mediastinal disorders," and numbers were similar in the bisoprolol group (12 of 259 [4.6%]) and placebo group (16 of 256 [6.3%]) (eTable 9 in Supplement 1).

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, antibiotics, or both 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 that of 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 most deaths in the metoprolol group were attributed to COPD.[15] BLOCK COPD also reported significant increases in breathlessness and COPD Assessment Test scores with use of metoprolol. In BICS, bisoprolol was not associated with an increase in COPD hospitalization or COPD Assessment Test score, and most deaths in the bisoprolol group were not attributed to COPD. However, similar to BLOCK COPD, BICS found that bisoprolol was associated with increased Transition Dyspnea Index–quantified breathlessness compared with

Table 2. Secondary Outcomes for Patients Randomized to Bisoprolol and Placebo

	FEV_1 % predicted			CAT score[a]			TDI[b]		
	Bisoprolol, %	Placebo, %	Adjusted mean difference (95% CI)[c]	Bisoprolol, %	Placebo, %	Adjusted mean difference (95% CI)[c]	Bisoprolol	Placebo	Adjusted mean difference (95% CI)[d]
Baseline									
Mean (SD) [No.]	49.3 (19.0) [256]	51.3 (19.1) [251]	NA	22.7 (8.12) [259]	22.0 (8.04) [255]	NA	NA	NA	NA
26 wk									
Mean (SD) [No.]	47.8 (18.8) [92]	47.0 (19.3) [87]	−0.75 (−3.61 to 2.10)	20.3 (8.85) [219]	18.7 (9.25) [222]	1.64 (0.05 to 3.23)	−0.83 (2.78)	−0.34 (2.91)	−0.62 (−1.16 to −0.07)
P value			.61			.04			.03
52 wk									
Mean (SD) [No.]	43.3 (20.8) [30]	53.1 (18.9) [21]	−4.53 (−10.2 to 1.16)	19.4 (8.86) [207]	19.8 (9.40) [202]	−0.59 (−2.26 to 1.07)	−1.73 (3.66)	−1.01 (3.58)	−0.73 (−1.44 to −0.01)
P value			.13			.48			.05

Abbreviations: CAT, COPD Assessment Test; FEV_1, forced expiratory volume in the first second of expiration; NA, not applicable; TDI, Transition Dyspnea Index.

[a] COPD Assessment Test: scale 0 to 40, with higher scores indicative of a greater effect of chronic obstructive pulmonary disease (COPD) on health and well-being; minimal clinically important difference (MCID) = 2 units.

[b] Transition Dyspnea Index: scale −9 to 9, with lower scores indicative of worse breathlessness; MCID = 1 unit. Mean difference represents overall mean difference between bisoprolol and placebo.

[c] Adjusted for center (as a random effect), recruitment setting (primary or secondary care), age centered on the mean, sex, smoking status (current vs former), FEV_1 percentage predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, and treatment with long-term antibiotics.

[d] Adjusted for center (as a random effect), recruitment setting (primary or secondary care), age centered on the mean, sex, smoking status (current vs former), FEV_1 percentage predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long-term antibiotics, and Baseline Dyspnea Index.

placebo, although the effect was small and the 95% CI was wide (−1.44 to −0.01). The differences in outcomes between BICS and BLOCK COPD may be because BLOCK COPD patients had more severe COPD (mean FEV_1, 40% vs 50% predicted; long-term oxygen use, 40% vs 5%), concomitant long-acting muscarinic antagonist was used less frequently (73% vs 90%), and there may have been more cardiovascular comorbid conditions (coronary artery disease, 15% vs 4%; hypertension, 46% vs 30%; and diabetes, 16% vs 11%). Also, the β-blocker used in BLOCK COPD (metoprolol) has a lower β_1:β_2 selectivity ratio compared with bisoprolol used in BICS.[15,31-33] The significance of concomitant long-acting muscarinic antagonist therapy was illustrated by Jabbal et al,[34] 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 5 mg while taking concomitant beclomethasone/formoterol or beclomethasone/formoterol with the long-acting muscarinic antagonist tiotropium.

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 United Kingdom. The high rate of triple (inhaled corticosteroid/long-acting β_2-agonist/long-acting muscarinic antagonist) inhaled therapy (74%) reflects best guideline-based practice in UK primary care for the treatment of people with COPD at high risk of exacerbation. Primary COPD exacerbation outcome data were available for 514 of the 515 patients (99.8%), likely due to the increased use of virtual (video or telephone) follow-up during the COVID-19 pandemic. To mitigate the issue that any potentially beneficial effect of bisoprolol was a consequence of treating ischemic heart disease, BICS excluded patients with guideline-recommended indications for β-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. Although 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 5 mg daily, and 18% could not tolerate bisoprolol during titration. Fifth, 31% of study patients took less than 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, according to 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.

Conclusions

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, antibiotics, or both.

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