ORIGINAL ARTICLE

Metoprolol for the Prevention of Acute Exacerbations of COPD

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ABSTRACT

BACKGROUND

Observational studies suggest that beta-blockers may reduce the risk of exacerbations and death in patients with moderate or severe chronic obstructive pulmonary disease (COPD), but these findings have not been confirmed in randomized trials.

METHODS

In this prospective, randomized trial, we assigned patients between the ages of 40 and 85 years who had COPD to receive either a beta-blocker (extended-release metoprolol) or placebo. All the patients had a clinical history of COPD, along with moderate airflow limitation and an increased risk of exacerbations, as evidenced by a history of exacerbations during the previous year or the prescribed use of supplemental oxygen. We excluded patients who were already taking a beta-blocker or who had an established indication for the use of such drugs. The primary end point was the time until the first exacerbation of COPD during the treatment period, which ranged from 336 to 350 days, depending on the adjusted dose of metoprolol.

RESULTS

A total of 532 patients underwent randomization. The mean (±SD) age of the patients was 65.0±7.8 years; the mean forced expiratory volume in 1 second (FEV_1) was 41.1±16.3% of the predicted value. The trial was stopped early because of futility with respect to the primary end point and safety concerns. There was no significant between-group difference in the median time until the first exacerbation, which was 202 days in the metoprolol group and 222 days in the placebo group (hazard ratio for metoprolol vs. placebo, 1.05; 95% confidence interval [CI], 0.84 to 1.32; P=0.66). Metoprolol was associated with a higher risk of exacerbation leading to hospitalization (hazard ratio, 1.91; 95% CI, 1.29 to 2.83). The frequency of side effects that were possibly related to metoprolol was similar in the two groups, as was the overall rate of nonrespiratory serious adverse events. During the treatment period, there were 11 deaths in the metoprolol group and 5 in the placebo group.

CONCLUSIONS

Among patients with moderate or severe COPD who did not have an established indication for beta-blocker use, the time until the first COPD exacerbation was similar in the metoprolol group and the placebo group. Hospitalization for exacerbation was more common among the patients treated with metoprolol. (Funded by the Department of Defense; BLOCK COPD ClinicalTrials.gov number, NCT02587351.)

CHRONIC OBSTRUCTIVE PULMONARY DIS-
ease (COPD) is the third leading cause of
death worldwide. Most of COPD-related
morbidity, mortality, and health care costs are
driven by exacerbations, particularly those lead-
ing to hospitalization.[1,2] Since many patients have
such exacerbations despite maintenance therapy,
new approaches to treatment are needed.[2]

An exacerbation of COPD may be triggered or
made more severe by underlying cardiovascular
disease.[3] Patients with COPD have up to five
times the risk of cardiovascular disease as age-
matched controls,[4] and cardiovascular disease
has been shown to be a risk factor for COPD
exacerbations,[5] hospitalization for exacerbations,[6]
in-hospital death,[7,8] and reduced survival.[9,10]

It is well established that beta-blockers reduce
mortality in patients after myocardial infarction[11]
and in those with heart failure.[12] Patients with
COPD are often not treated with this class of
medications, even when they have an evidence-
based indication for the use of such drugs, be-
cause of concern about possible adverse effects
on lung function.[13,14] This practice pattern persists
despite multiple observational studies suggesting
that beta-blockers benefit patients with COPD
and coexisting cardiovascular disease, with out-
comes similar to those observed in patients
without COPD.[13,15,16] Several nonrandomized ob-
servational studies involving patients with COPD
have also suggested that beta-blockers reduce
the risk of exacerbations and death, regardless
of the presence of cardiac disease.[17-20] However,
these observational data are subject to biases,
which has precluded determinations regarding
cause and effect.[21]

In the BLOCK COPD (Beta-Blockers for the
Prevention of Acute Exacerbations of Chronic
Obstructive Pulmonary Disease) trial, we inves-
tigated the effect of the beta-blocker metoprolol,
as compared with placebo, on the risk of COPD
exacerbations among patients who were at high
risk for such events.[22] We hypothesized that the
use of metoprolol would lower the risk of exac-
erbations in these patients without having an
adverse effect on lung function, results on a
6-minute walk test, dyspnea, or quality of life.

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted this placebo-controlled, double-
blind, prospective, randomized trial at 26 centers
in the United States. The trial protocol, which
was approved by the data and safety monitoring
committee and the institutional review board at
each trial center, is available with the full text
of this article at NEJM.org. The Department of
Defense funded the trial but had no role in its
design, in the accrual or analysis of the data, or
in the preparation of the manuscript. No com-
mercial entity was involved in the trial. Written
informed consent was obtained from all the
patients.

INCLUSION AND EXCLUSION CRITERIA

We enrolled patients between the ages of 40 and
85 years who had received a clinical diagnosis of
COPD and who had at least moderate airflow
limitation, as defined by the Global Initiative for
Obstructive Lung Disease (GOLD),[2] as follows:
a forced expiratory volume in 1 second (FEV_1) of
less than 80% of the predicted value after bron-
chodilation and a ratio of the FEV_1 to the forced
vital capacity (FVC) of less than 0.70. We re-
cruited patients who were at increased risk for
exacerbations as indicated by at least one of the
following factors: the receipt of a course of sys-
temic glucocorticoids or antibiotic agents for
respiratory problems during the previous year, a
visit to an emergency department or hospitaliza-
tion for a COPD exacerbation during the previous
year, or the receipt of a prescription for supple-
mental oxygen for use at home for the treatment
of COPD. The inclusion criteria were a resting
heart rate between 65 and 120 beats per minute
and a resting systolic blood pressure of more
than 100 mm Hg. We excluded patients who had
a proven indication for the use of a beta-blocker,
including a history of myocardial infarction or
revascularization within the previous 36 months
or heart failure with a known left ventricular
ejection fraction of less than 40%.[23,24]

RANDOMIZATION AND INTERVENTION

Randomization was performed by a computer
algorithm by means of an interactive website
linked to the data coordinating center. The
starting dose was one 50-mg tablet of metopro-
lol or matching placebo taken orally daily. Meto-
prolol was purchased for use in the trial; match-
ing placebo was manufactured at the Current
Good Manufacturing Practices Facility at the
Temple University School of Pharmacy. For 42
days after randomization, patients underwent a
dose-adjustment period on the basis of their

heart rate, systolic blood pressure, changes in FEV_1, and assessment of possible beta-blocker side effects. This dose adjustment resulted in a final daily dose of 25 mg, 50 mg, or 100 mg. Patients were followed until completion of the day 336 visit, after which they were weaned off either metoprolol or placebo, and were monitored for symptoms of beta-blocker withdrawal until the day 378 visit.

PRIMARY AND SECONDARY END POINTS

The primary end point was the median time until the first COPD exacerbation of any severity during the treatment period, which was defined as the period from randomization to day 336 for the patients receiving a final dose of 25 mg of metoprolol or placebo or until day 350 for those receiving a dose of 50 mg or 100 mg. This difference in treatment period according to dose was due to the additional time necessary to wean patients from the 50-mg and 100-mg dose levels.

An exacerbation of COPD was defined as an increase in or a new onset of two or more of the following symptoms: cough, sputum production, wheezing, dyspnea, or chest tightness that led to treatment with antibiotics or systemic glucocorticoids for at least 3 days.[25,26] The severity of the exacerbation was graded according to the following scale: mild (involving only home management, with or without contact with a health care provider), moderate (leading to a visit to an emergency department), severe (leading to hospitalization), and very severe (leading to intubation and mechanical ventilation). Key secondary end points included the rate of COPD exacerbations, all-cause mortality, all-cause hospitalization, results of spirometry, distance on the 6-minute walk test, dyspnea assessments, and measures of quality of life.

TRIAL VISITS

During in-clinic visits and telephone calls, the patients were queried regarding the efficacy and safety of the trial treatment, including providing details regarding any possible beta-blocker side effects. Spirometry and 6-minute walk tests were performed according to American Thoracic Society–European Respiratory Society guidelines.[27,28] Data regarding spirometry that was performed after bronchodilation are presented as a percentage of predicted reference values.[29] We evaluated the patients' disease-specific quality of life using scores on the St. George's Respiratory Questionnaire[30] and the COPD Assessment Test[31] and assessed the level of dyspnea using the modified Medical Research Council (mMRC) scale[32] and the San Diego Shortness of Breath Questionnaire[33] (SOBQ). In addition, we measured the 6-minute walk distance at baseline, at the day 112 visit, and at the day 336 visit. (Scores on the St. George's Respiratory Questionnaire range from 0 to 100, with lower scores indicating better functioning and with a minimal clinically important difference [MCID] of 4 points.[30] Scores on the COPD Assessment Test range from 0 to 40, with lower scores indicating better functioning and with a MCID of 2 points.[31] Scores for dyspnea on the mMRC scale range from 0 to 4, with higher scores indicating more severe breathlessness.[32] Scores on the San Diego Shortness of Breath Questionnaire range from 0 to 120, with higher scores indicating more severe breathlessness and with an MCID of 5 points.[33])

MONITORING PLAN, INTERIM ANALYSIS, AND EARLY TERMINATION

The data and safety monitoring committee met approximately every 6 months to review recruitment, follow-up rates, safety, and efficacy results. Reviews of outcome data involved multiple statistical testing procedures performed on a set of accumulating data, with the use of a sequential monitoring plan based on the alpha spending approach.[34]

After the first interim analysis on November 30, 2018, the committee recommended that the trial be continued but planned to reconvene before the second interim analysis to review serious adverse events. On March 21, 2019, the committee recommended that the trial be stopped on the basis of the conditional power analyses and concern about safety. (Details regarding the power analyses are provided in the Supplementary Appendix, available at NEJM.org.) Patients who had not yet completed the day 336 visit were contacted early to undergo final assessments and begin weaning from metoprolol or placebo, according to the protocol.

STATISTICAL ANALYSIS

We based the sample size and considerations for statistical power on the primary end point of the time until the first exacerbation of COPD. On the basis of data from previous clinical trials of a similar design,[25,26] we estimated that 65% of the patients in the placebo group would have an

exacerbation during the 1-year trial and that metoprolol would reduce this risk to 55%. Sample-size calculations that included a two-sided alpha level of 0.05 and a trial power of 90% indicated we would need to enroll 1028 patients on the assumption of a loss to follow-up of approximately 12%.

The primary analysis was based on Kaplan–Meier survival curves that described the probability of remaining exacerbation-free in each of the two groups. We used the log-rank test to compare the two curves. As secondary analyses, we used both unadjusted and adjusted Cox proportional-hazards models to assess the association between the trial-group assignment and the time until the first COPD exacerbation. Adjusted models included the covariates of race, sex, baseline age, FEV_1 as a percentage of the predicted value, smoking status, heart rate greater than the median value, number of hospitalizations for COPD during the previous year, number of exacerbations treated with glucocorticoids or antibiotics during the previous year, use of supplemental oxygen, scores on the COPD Assessment Test and the mMRC scale, and trial center.

We used Kaplan–Meier methods and Cox models to perform similar analyses of overall survival and used negative binomial regression models to analyze exacerbation rates. We used Student's t-tests to compare annualized rates of hospitalization and nonfatal serious adverse events and used mixed-effects models with patient-specific random intercepts to compare between-group differences in changes in continuous measures of secondary end points. All the analyses are based on the intention-to-treat principle.

RESULTS

PATIENTS

From May 2016 through March 2019, a total of 532 patients underwent randomization (268 to the metoprolol group and 264 to the placebo group). The most common reasons for exclusion were not meeting the spirometric criteria for COPD or a resting heart rate that was out of the mandated range. Details regarding screening, randomization, and follow-up are provided in Figure 1.

The demographic and clinical characteristics of the patients at baseline are provided in Table 1, with a full list provided in Table S1 in the Supplementary Appendix. The mean (±SD) age of the patients was 65.0±7.8 years, the mean FEV_1 was 41.1±16.3% of the predicted value, and the mean smoking exposure was 50.1±29.1 pack-years.

COPD EXACERBATIONS

There was no significant between-group difference in the median time until the first exacerbation, which was 202 days (95% confidence interval [CI], 162 to 282) in the metoprolol group and 222 days (95% CI, 189 to 295) in the placebo group (Fig. 2A). The unadjusted hazard ratio for the comparison between metoprolol and placebo was 1.05 (95% CI, 0.84 to 1.32; P=0.66), which was similar after adjustment (hazard ratio, 1.12; 95% CI, 0.88 to 1.42). For the time until the first exacerbation of moderate severity or greater, the unadjusted hazard ratio was 1.47 (95% CI, 1.06 to 2.04) and the adjusted hazard ratio was 1.46 (95% CI, 1.03 to 2.06) (Fig. S1A). For severe or very severe exacerbations, the unadjusted and adjusted hazard ratios were 1.91 (95% CI, 1.29 to 2.83) and 2.08 (95% CI, 1.37 to 3.14), respectively (Fig. 2B). The result of the subgroup analysis of the risk of exacerbation is provided in Figure S2.

We found no evidence of a between-group difference in the overall rates of exacerbation, with a rate per person-year of 1.40 (95% CI, 1.21 to 1.61) in the metoprolol group and 1.33 (95% CI, 1.15 to 1.54) in the placebo group (rate ratio, 1.05; 95% CI, 0.85 to 1.28). There was evidence that the metoprolol group had a higher rate of more severe exacerbation than the placebo group, with a rate ratio of 1.51 (95% CI, 1.00 to 2.29) for severe exacerbation and 3.71 (95% CI, 1.10 to 16.98) for very severe exacerbation (Table 2 and Fig. S3).

MORTALITY

During the treatment period, there were 11 deaths in the metoprolol group and 5 in the placebo group, with unadjusted and adjusted hazard ratios for death of 2.18 (95% CI, 0.76 to 6.29) and 2.13 (95% CI, 0.69 to 6.42), respectively (Fig. S1B). The majority of deaths in the metoprolol group were attributed to COPD (7, vs. 1
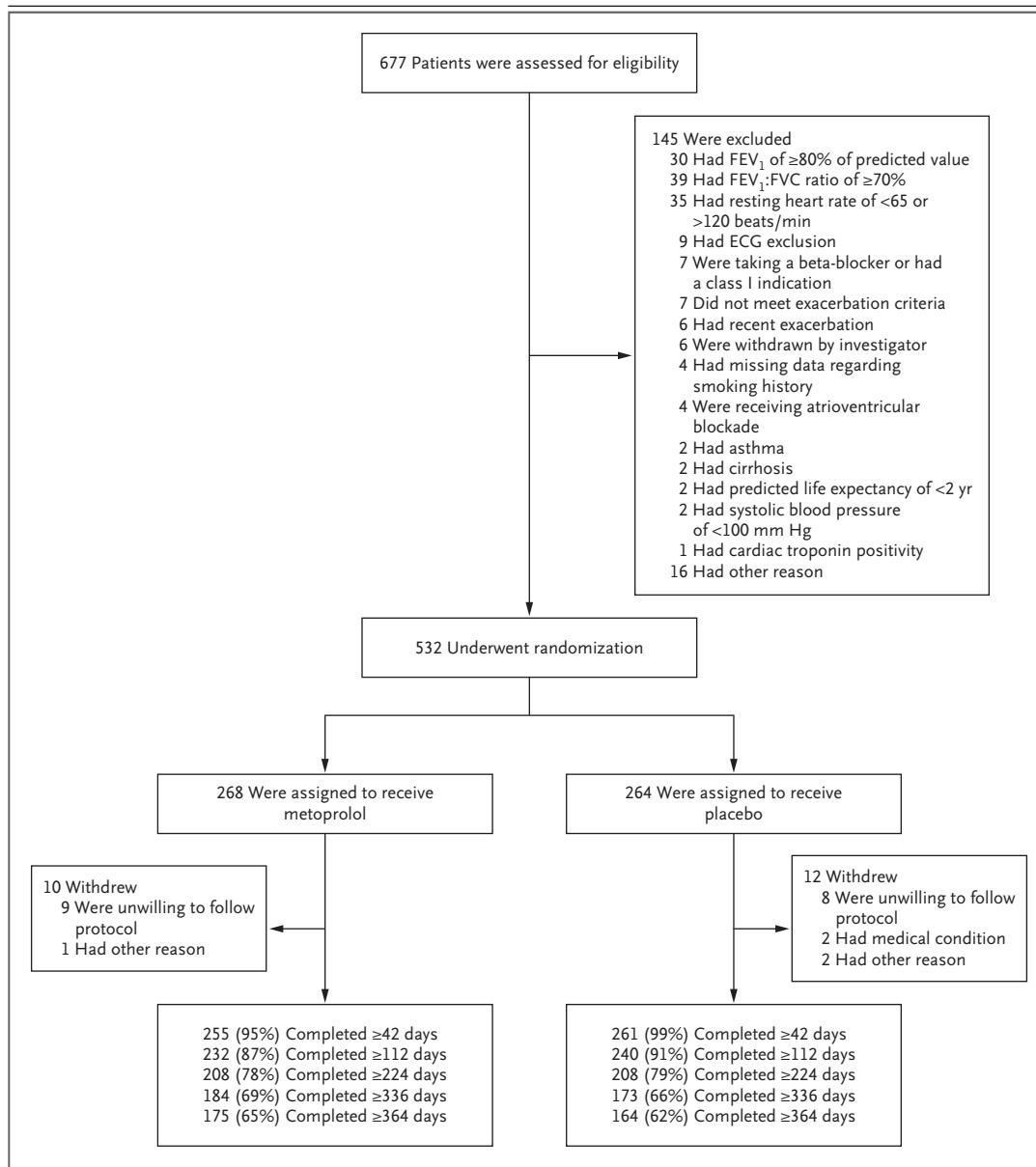
Figure 1. Screening, Randomization, and Follow-up.

Among the 145 patients who were excluded from the trial, several had more than one reason for exclusion. Patients were excluded from the trial if they had a class I indication for receipt of a beta-blocker (a history of myocardial infarction or revascularization within the previous 36 months or heart failure with a known left ventricular ejection fraction of less than 40%), according to the guidelines of the American College of Cardiology and the American Heart Association. ECG denotes electrocardiography, FEV_1 forced expiratory volume in 1 second, and FVC forced vital capacity.

in the placebo group) (Table 3). After the treatment period, there were 3 additional deaths in the metoprolol group (at 10 to 277 days after the last dose) and 4 additional deaths in the placebo group (at 10 to 26 days after the last dose).

HOSPITALIZATION AND NONFATAL SERIOUS ADVERSE EVENTS

The rate of hospitalization for any cause was 0.66 per person-year (95% CI, 0.47 to 0.86) in the metoprolol group and 0.42 per person-year

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Metoprolol (N = 268)	Placebo (N = 264)
Age — yr	65.2±7.6	64.8±7.9
Race — no. (%)†		
White	178 (66.4)	194 (73.5)
Black	83 (31.0)	60 (22.7)
Other	7 (2.6)	10 (3.8)
Female sex — no. (%)	124 (46.3)	123 (46.6)
FEV$_1$ after bronchodilation — % of predicted value	41.3±16.3	40.8±16.2
FEV$_1$:FVC ratio — %	44.2±11.7	45.2±21.6
Smoking history		
No. of pack-yr	50.7±28.7	49.5±29.6
Current smoker — no. (%)	95 (35.4)	71 (26.9)
COPD medication — no. (%)		
Inhaled glucocorticoid, LABA, and LAMA	154 (57.5)	160 (60.6)
Inhaled glucocorticoid and LABA	45 (16.8)	51 (19.3)
LAMA only	20 (7.5)	17 (6.4)
LABA and LAMA	11 (4.1)	13 (4.9)
Inhaled glucocorticoid and LAMA	8 (3.0)	6 (2.3)
Inhaled glucocorticoid only	5 (1.9)	2 (0.8)
Other	25 (9.3)	15 (5.7)
Heart rate — beats/min	85.5±10.8	83.6±11.7
Blood pressure — mm Hg		
Systolic	128.4±16.5	130.6±15.9
Diastolic	77.2±9.2	76.8±9.1
No. of courses of systemic glucocorticoids or antibiotic use in previous 12 mo	1.9±1.5	1.9±1.7
No. of hospitalizations in previous 12 mo	0.7±1.0	0.5±1.2
Score on COPD Assessment Test‡	20.1±7.3	21.3±7.3
Score of >1 on modified Medical Research Council scale — no. (%)§	164 (61.2)	169 (64.0)
Enrollment criteria — no. (%)		
Systemic glucocorticoid or antibiotic use in previous 12 mo	246 (91.8)	228 (86.4)
COPD exacerbation leading to emergency department visit or hospitalization in previous 12 mo	168 (62.7)	133 (50.4)
Prescription or use of supplemental oxygen in previous 12 mo	106 (39.6)	106 (40.2)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. COPD denotes chronic obstructive pulmonary disease, FEV$_1$ forced expiratory volume in 1 second, FVC forced vital capacity, LABA long-acting beta agonist, and LAMA long-acting muscarinic antagonist.
† Race was reported by the patients.
‡ Scores on the COPD Assessment Test range from 0 to 40, with lower scores indicating better functioning and with a minimal clinically important difference of 2 points.
§ Scores for dyspnea on the modified Medical Research Council scale range from 0 to 4, with higher scores indicating more severe breathlessness.

(95% CI, 0.30 to 0.55) in the placebo group. The rate of overall nonfatal serious adverse events was 0.65 per person-year in the metoprolol group and 0.43 per person-year in the placebo group. Nonfatal, serious COPD exacerbations occurred at a rate of 0.43 per person-year and 0.19 per person-year, respectively (Table 3 and Table S2).
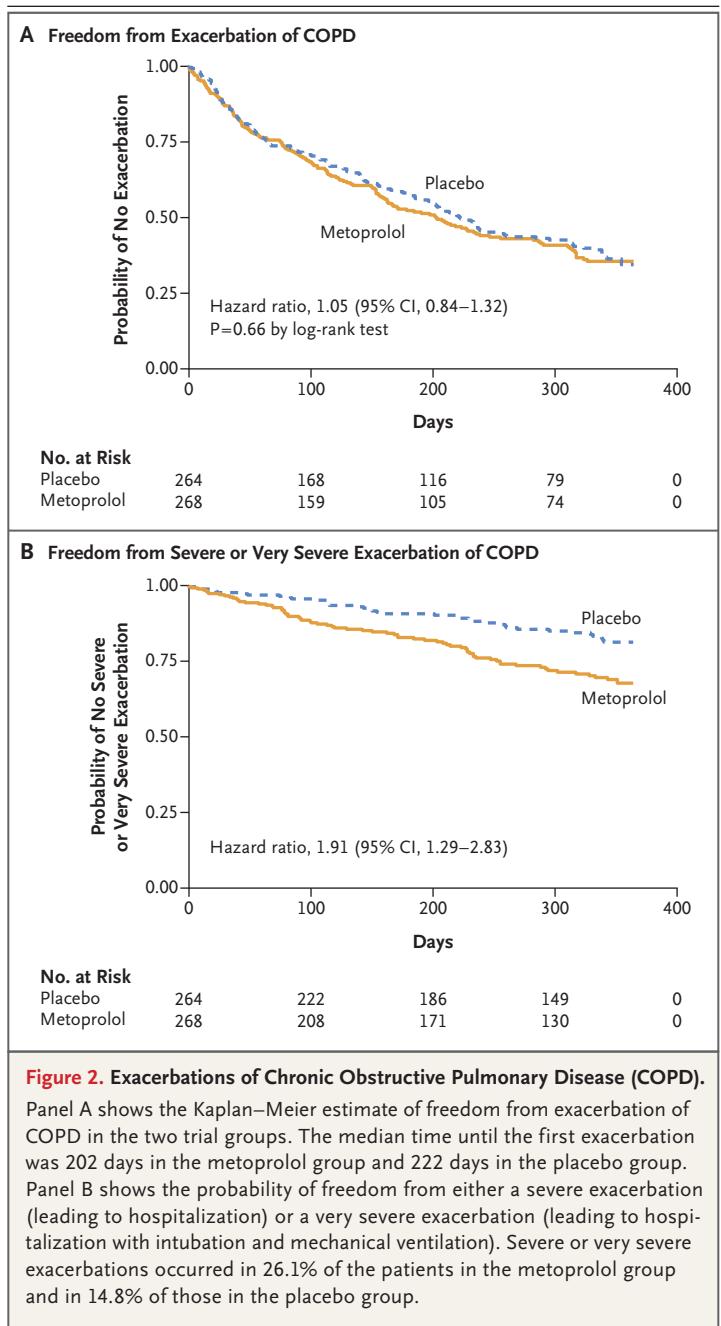
OTHER PRESPECIFIED MEASURES

There were no significant between-group differences in several prespecified measurements, including the change from baseline in the FEV_1, in the 6-minute walk distance, and in the score on the St. George's Respiratory Questionnaire (Figs. S4, S5, and S6). The patients in the metoprolol group had a greater increase (indicating worse control) from baseline in the score on the COPD Assessment Test than those in the placebo group, with a difference of 1.13 points (95% CI, 0.06 to 2.20) at day 112 and a difference of 1.47 points (95% CI, 0.32 to 2.62) at day 336 (Fig. S7). The metoprolol group also had a greater increase in SOBQ scores from baseline, indicating a worsening in shortness of breath. The between-group difference in the change from baseline was 3.47 points (95% CI, 0.42 to 6.52) at day 112 and 4.80 points (95% CI, 1.52 to 8.07) at day 336 (Fig. S8).

ADVERSE EVENTS AND DISCONTINUATIONS

We observed no evidence of between-group differences in the frequency of patient-reported adverse events that were potentially related to metoprolol (Table S3). Patients in the metoprolol group had a lower mean heart rate than those in the placebo group (difference, 6 to 10 beats per minute) (Fig. S9). Smaller and less consistent effects were seen for systolic and diastolic blood pressure. The discontinuation of metoprolol or placebo occurred more frequently in the metoprolol group than in the placebo group (11.2% vs. 6.1%). The most common reason for discontinuation was an increase in respiratory symptoms (Table S4).

DISCUSSION

In this prospective, multicenter, randomized trial, we did not find evidence of a difference in the

Figure 2. Exacerbations of Chronic Obstructive Pulmonary Disease (COPD).
Panel A shows the Kaplan–Meier estimate of freedom from exacerbation of COPD in the two trial groups. The median time until the first exacerbation was 202 days in the metoprolol group and 222 days in the placebo group. Panel B shows the probability of freedom from either a severe exacerbation (leading to hospitalization) or a very severe exacerbation (leading to hospitalization with intubation and mechanical ventilation). Severe or very severe exacerbations occurred in 26.1% of the patients in the metoprolol group and in 14.8% of those in the placebo group.

risk of COPD exacerbation between the metoprolol group and the placebo group, although the use of metoprolol was associated with a higher risk of exacerbation leading to hospitalization. These results differ from previously reported findings from observational studies suggesting that beta-blockers reduce the risks of exacerba-

Table 2. Rate of Exacerbation of COPD, According to Severity.

Severity of Exacerbation	Metoprolol (N = 268)		Placebo (N = 264)		Rate Ratio (95% CI)
	Events	Rate (95% CI)	Events	Rate (95% CI)	
	no.	*no. of events/person-yr*	*no.*	*no. of events/person-yr*	
Any severity	289	1.40 (1.21–1.61)	272	1.33 (1.15–1.54)	1.05 (0.85–1.28)
Mild	163	0.78 (0.65–0.94)	178	0.88 (0.74–1.05)	0.89 (0.69–1.15)
Moderate	34	0.17 (0.11–0.25)	36	0.18 (0.12–0.26)	0.94 (0.53–1.65)
Severe	81	0.40 (0.30–0.52)	55	0.26 (0.19–0.36)	1.51 (1.00–2.29)
Very severe	11	0.05 (0.03–0.10)	3	0.01 (0.00–0.05)	3.71 (1.10–16.98)
Moderate or greater	126	0.62 (0.50–0.77)	94	0.45 (0.35–0.58)	1.36 (0.98–1.91)
Severe or very severe	92	0.45 (0.35–0.58)	58	0.28 (0.21–0.38)	1.63 (1.10–2.42)

Table 3. Nonfatal and Fatal Serious Adverse Events.*

Event	Metoprolol (N = 268)	Placebo (N = 264)	P Value†
Nonfatal adverse events — no. of events per person-yr‡			
All events	0.650	0.430	0.07
Cardiovascular event			
Myocardial infarction	0.009	0.004	0.51
Heart failure	0.008	0.014	0.57
Stroke	0.004	0.008	0.65
Arrhythmias	0.012	0.008	0.71
Hypotension	0	0.004	0.31
Other cardiovascular event	0.004	0.004	0.99
Respiratory event			
COPD exacerbation§	0.430	0.190	0.02
Pneumonia	0.084	0.057	0.34
Other respiratory event	0.020	0.004	0.16
Fatal events — no. of patients (%)¶			
All events	11 (4.1)	5 (1.9)	0.14
COPD	7 (2.6)	1 (0.4)	—
Sudden cardiac death	0	1 (0.4)	—
Lung cancer	1 (0.4)	0	—
Sepsis	1 (0.4)	1 (0.4)	—
Unknown	1 (0.4)	2 (0.8)	—
Other	1 (0.4)	0	—

* Listed are adverse events that were reported as serious by the investigator.
† For nonfatal adverse events, P values were calculated by Student's t-test. For fatal adverse events, the P value for the overall between-group comparison was calculated by the log-rank test; P=0.17 by Fisher's exact test for the overall comparison among the causes of death.
‡ Nonfatal events are reported as rates per person-year because the patients could have had more than one event. A complete list of nonfatal serious adverse events is provided in Table S2.
§ COPD exacerbations that are listed here may not meet the protocol-defined criteria for the primary end point.
¶ After the treatment period, three additional deaths occurred in the metoprolol group (two from COPD and one from pneumonia) and four in the placebo group (one from COPD, one from lung cancer, and two from unknown causes).

tion and death from any cause in patients with COPD.[17-19] A meta-analysis of 9 studies showed that patients taking beta-blockers had a lower risk of COPD-related death than those not taking beta-blockers (relative risk, 0.69; 95% CI, 0.62 to 0.78).[18] Another meta-analysis of 15 studies also showed a lower risk of death from any cause (relative risk, 0.72; 95% CI, 0.63 to 0.83) or from COPD exacerbation (relative risk, 0.63; 95% CI, 0.57 to 0.71).[19] These observational studies have methodologic limitations inherent to their design, including the possibility of residual confounding and immortal time bias, which may have had an effect on the findings.[21]

A primary concern about the use of beta-blockers in patients with COPD is that the drugs may cause a worsening in lung function. We did not observe this effect, and none was reported in a meta-analysis on the subject.[35] We also found no evidence of between-group differences in the 6-minute walk distance or in patients' reports of possible beta-blocker side effects. However, metoprolol was associated with worsening of dyspnea and of the overall burden of COPD symptoms, as measured by the shortness-of-breath questionnaire and the COPD Assessment Test (although not on the St. George's Respiratory Questionnaire). In addition, more discontinuations occurred in the metoprolol group than in the placebo group, which suggests the presence of adverse respiratory effects not captured by spirometry.

Our trial has several limitations. First, although the investigators and patients were unaware of trial-group assignments, it was not possible to fully blind the effects of beta blockade, which resulted in reductions in heart rate and blood pressure. Second, our trial population had moderate or severe COPD with a high prevalence of supplemental oxygen use and previous hospitalization for COPD. Thus, we do not know whether our results would apply to patients with mild airflow obstruction or a lower exacerbation risk. Third, in part because the trial was stopped early, we had limited power to detect differences in the risk of severe exacerbation between subgroups and could not identify specific factors that predisposed patients to adverse outcomes when treated with metoprolol. Fourth, we do not know whether these results would be similar for other cardioselective beta-blockers or for non-cardioselective agents, although concern regarding adverse respiratory effects is greater with the latter.[36] Finally, we did not enroll patients who had a proven indication for the use of a beta-blocker or who were already taking the drugs, so our results do not inform the risk of COPD exacerbations with metoprolol in such patients.

The risk of exacerbations of COPD was similar in the metoprolol group and the placebo group among patients with moderate or severe COPD who were at increased risk for exacerbations and had no proven indication for beta-blockers. Although observational studies have suggested that the benefits of beta-blockers in patients with recent myocardial infarction and heart failure extend to those with COPD,[15,19] this hypothesis has not been prospectively confirmed, and randomized trials to determine the overall risk–benefit ratio in such patients may be needed.

APPENDIX

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