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AZITHROMYCIN DURING ACUTE CHRONIC OBSTRUCTIVE PULMONARY DISEASE EXACERBATIONS REQUIRING HOSPITALIZATION (BACE)

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

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ABSTRACT

Rationale: Azithromycin prevents acute exacerbations of chronic obstructive pulmonary disease (AECOPDs); however, its value in the treatment of an AECOPD requiring hospitalization remains to be defined.

Objectives: We investigated whether a 3-month intervention with low-dose azithromycin could decrease treatment failure (TF) when initiated at hospital admission and added to standard care.

Methods: In an investigator-initiated, multicenter, randomized, double-blind, placebo-controlled trial, patients who had been hospitalized for an AECOPD and had a smoking history of !!! 10 pack-years and one or more exacerbations in the previous year were randomized (1:1) within 48 hours of hospital admission to azithromycin or placebo. The study drug (500 mg/d for 3 d) was administered on top of a standardized acute treatment of systemic corticosteroids and antibiotics, and subsequently continued for 3 months (250 mg/2 d). The patients were followed for 6 months thereafter. Time-to-first-event analyses evaluated the TF rate within 3 months as a novel primary endpoint in the intention-to-treat population, with TF defined as the composite of treatment intensification with systemic corticosteroids and/or antibiotics, a step-up in hospital care or readmission for respiratory reasons, or all-cause mortality.

Measurements and Main Results: A total of 301 patients were randomized to azithromycin ($n = 147$) or placebo ($n = 154$). The TF rate within 3 months was 49% in the azithromycin group and 60% in the placebo group (hazard ratio, 0.73; 95% confidence interval, 0.53-1.01; $P = 0.0526$). Treatment

intensification, step-up in hospital care, and mortality rates within 3 months were 47% versus 60% ($P = 0.0272$), 13% versus 28% ($P = 0.0024$), and 2% versus 4% ($P = 0.5075$) in the azithromycin and placebo groups, respectively. Clinical benefits were lost 6 months after withdrawal.

Conclusions: Three months of azithromycin for an infectious AECOPD requiring hospitalization may significantly reduce TF during the highest-risk period. Prolonged treatment seems to be necessary to maintain clinical benefits.

KEYWORDS: macrolide; composite; time to event; treatment failure; readmission

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject: Clinical trials in patients with stable chronic obstructive pulmonary disease (COPD) and those with an increased risk of exacerbations have shown that long-term (6-12 mo) continuous and intermittent use of macrolide antibiotics is effective in preventing acute exacerbations of COPD (AECOPDs). Because of safety concerns associated with long-term use in the general COPD population, however, new studies are needed to define the optimal dose, treatment duration, and target population.

What This Study Adds to the Field:

The present double-blind, randomized controlled trial is the first to evaluate the effect of macrolide treatment by positioning the intervention in the acute setting of a severe AECOPD requiring hospitalization, in addition to a time-limited low-dose intermittent administration to prevent relapse. Although the results were formally negative ($P = 0.0526$), our findings show that a low-dose azithromycin intervention initiated at the onset of a severe AECOPD requiring hospitalization (500 mg/d for 3 d) and subsequently administered for 3 months (250 mg/2 d) may strongly reduce the recurrence of exacerbations, especially those leading to hospital admission and transfer to intensive care, in patients at risk Prolonged treatment, however, appears to be needed to maintain clinical benefits. By providing a cross-continuum between the acute treatment phase in the hospital and ambulatory therapeutic prolongation for 3 months, the proposed intervention may help to address the highest-risk period for readmission and provide a new treatment strategy for a severe infectious AECOPD requiring hospitalization.

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Acute exacerbations of chronic obstructive pulmonary disease (AECOPDs) requiring hospitalization are associated with a 6% risk of in-hospital mortality. Thirty-five percent of the patients who survive are likely to be readmitted within 3 months after hospital discharge (with 80% of such readmissions being directly related to recurrent disease or relapse), during which time they face a 12% risk of all-cause mortality (1, 2). Therefore, the management of an AECOPD requiring hospitalization has been studied extensively (3, 4). However, with the exception of noninvasive ventilation administered to patients with acute respiratory acidosis (5), no intervention has been shown to improve the prognosis over the last 40 years (6).

Long-term treatment with 250 mg azithromycin once daily has proved to be effective in preventing AECOPDs by decreasing the exacerbation rate and increasing the interexacerbation interval (7, 8). Although the efficacy of an intermittent dose (500 mg three times weekly) was confirmed in a restricted subgroup of frequent exacerbators (9), safety concerns associated with long-term use in the general COPD population (10), such as the induction of antibiotic resistance (11), cardiac toxicity (12), and ototoxicity (13), necessitate new studies to define the optimal dose, treatment duration, and target population.

Published randomized controlled trials (RCTs) of azithromycin therapy in COPD have focused exclusively on subjects with stable disease and an increased risk of exacerbations. Currently, few RCTs are evaluating new acute interventions in patients hospitalized for a severe exacerbation, facing the highest-risk period for deterioration, relapse, and death. Therefore, we performed a large investigator-initiated RCT to evaluate whether a 3-month intervention with low-dose azithromycin, initiated at the onset of a severe AECOPD requiring hospitalization, could effectively and safely decrease treatment failure (TF) in the highest-risk period during and immediately after an acute event. Using time-to-first-event analyses, we evaluated TF as a novel composite primary endpoint to capture clinically relevant short-term and long-term outcomes of our intervention. Some of the results of this study have been previously reported in the form of an abstract (14).

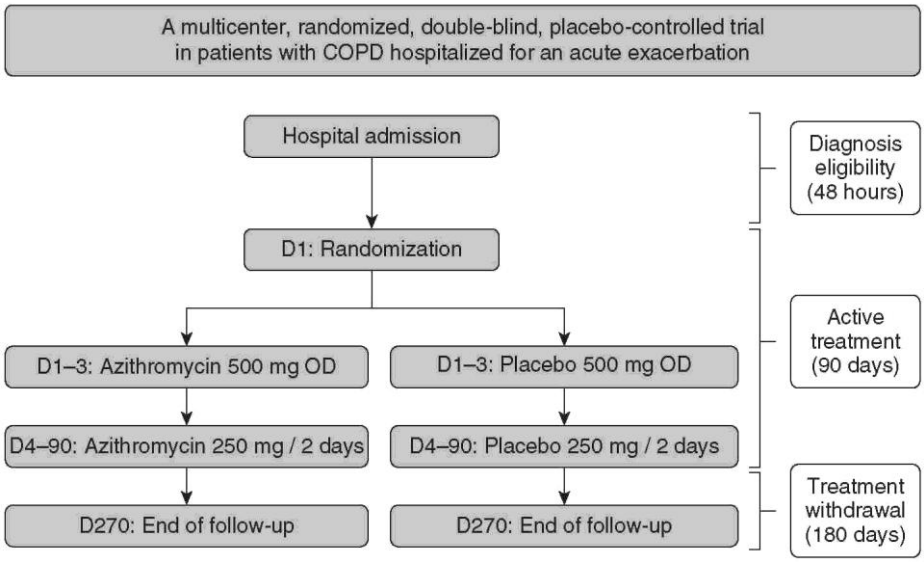
Methods

STUDY DESIGN

An investigator-initiated, multicenter, randomized, double-blind, placebo-controlled trial was performed in 6 academic and 14 nonacademic hospitals in Belgium to investigate the effectiveness of azithromycin in the acute treatment of COPD exacerbations requiring hospitalization. Between August 2014 and April 2017, patients were randomized (1:1) to receive azithromycin or placebo on top of a standardized acute treatment of systemic corticosteroids and antibiotics (online supplement). Within 48 hours of hospital admission, a 3-month (or 90-d) intervention with azithromycin or matching placebo was initiated at a loading dose of 500 mg once daily for 3 days (which was hypothesized to maximize both acute antimicrobial and antiinflammatory effects) and subsequently administered at a lower intermittent maintenance dose of 250 mg every 2 days (which was hypothesized to prolong antiinflammatory effects). Patients were followed for 9 months, including 6 months after study drug withdrawal, to evaluate whether potential effects of the 3-month intervention could be maintained long term (Figure 1) (15). The study included three assessments during hospitalization of the index event: randomization (Day 1), start of the maintenance dose (Day 4), and day of discharge (Day X, at the investigator's discretion). After discharge, outpatient visits occurred at 1 month after discharge (Day X + 28), the end of intervention (Day 90), and the end of follow-up (Day 270). Telephone calls were scheduled bimonthly (Days 150 and 210) between Day 90 and Day 270.

Written informed consent was obtained from all participants. The study was approved by the competent authorities and the central (Commissie Medische Ethiek UZ-KU Leuven, ML10232) and local ethics committees of each participating hospital. The clinical trial is registered with ClinicalTrials.gov (Identifier: NCT02135354; https://clinicaltrials.gov/).

Figure 1. *The BACE trial study design. BACE = Belgian trial with azithromycin for acute COPD exacerbations requiring hospitalization; COPD = chronic obstructive pulmonary disease; D1 =Day 1; D1 - 3 = Days 1 -3; D4-90 = Days 4-90; D270 = Day 270; OD = once a day.*



PATIENTS

Eligible patients were 18 years or older, had an established diagnosis of COPD (based on clinical history and a pulmonary function test), had a history of one or more exacerbations treated with systemic corticosteroids and/or antibiotics in the previous year, were current smokers or had a smoking history of !!!10 pack-years, had a normal QT interval corrected according to Bazett's formula (QTcB; ≤450 ms for males and ≤470 ms for females), and were hospitalized for an AECOPD that was deemed infectious by the local investigator within the 48-hour screening period from hospital admission, qualifying them for the standardized acute treatment of systemic corticosteroids and antibiotics. The investigators had to rely on the available evidence obtained from routine assessments (laboratory, chest X-ray, and clinical presentation) in the emergency department, as the trial protocol was embedded in a real-life hospitalization setting. The main exclusion criteria were contraindications to azithromycin, respiratory insufficiency requiring mechanical or noninvasive ventilation at the time of randomization, chronic systemic corticosteroid use (>4 mg methylprednisolone/d for ≥2 mo), and the use of macrolide antibiotics during ≥2 weeks preceding inclusion. Presentation of lobar pneumonia was an exclusion criterion. None of the patients were taking phosphodiesterase-4 inhibitors (which are not commercialized in Belgium). A full list of the exclusion criteria is provided in the online supplement.

EFFICACY OUTCOMES

The primary endpoint was the TF rate within 90 days, analyzed using time-to-first-event methods, with TF defined as the composite of three endpoints: *1)* treatment intensification (TI) with systemic corticosteroids and/or antibiotics for respiratory reasons; *2)* step-up in hospital care (SH), including

transfer to the ICU or readmission for respiratory reasons; and 3) all-cause mortality. The date of TF was defined as the time of the first occurrence of one of these events. TI and SH were further specified for the hospitalization period of the index event (Day 1 to Day X), and the period after discharge (Day X to Day 90), as outlined in Table 1. All TFs and their components were adjudicated on site by a centrally blinded investigator. Three key secondary endpoints were assessed in the following hierarchical order: the number of TFs, COPD assessment test (CAT) score, and total days of systemic corticosteroid use at Day 90. Other secondary endpoints, including evaluation of the composite endpoint and its three components 6 months after study drug withdrawal, are listed in the online supplement.

SAFETY OUTCOMES

Standard 12-lead resting ECGs, obtained at hospital admission (baseline), Day 4, Day X + 28, and Day 90 were inspected manually. The QT interval values were corrected using Bazett's formula (QTcB) and verified using Fridericia's formula (QTcF), reflecting a more accurate correction in patients with tachycardia (16). Safety outcomes also included the assessment of (serious) adverse events; the Speech, Spatial, and Qualities of Hearing Scale-5 items (SSQ5) questionnaire (17); and spontaneous sputum samples for detection of macrolide-resistant pathogens. Details are provided in the online supplement.

STATISTICAL ANALYSES

The required sample size was calculated at 250 patients per group, 500 in total, to show a significant difference in the primary endpoint at a two-sided significance level of 0.05 with 80% power. Calculations were based on a survival analysis using a log-rank test assuming proportional hazards, a clinical failure within 90 days of at least 45% in the placebo arm, a 35% relative improvement with azithromycin (hazard ratio [HR], 0.65) and taking into account a maximal dropout of 25%. Due to slow recruitment and unavailability of funds, it was decided to stop enrollment early at 301 inclusions (moment of interim safety analysis, prespecified after 300 inclusions), and the final analysis was performed once all patients reached their 270-day follow-up.

Table 1. *Definition of the Composite Primary Endpoint, Treatment Failure*

Components of the Composite	During Hospitalization of the Index Event (Day 1 to Day X)	After Hospital Discharge (Day X to Day 90)
1. Treatment intensification for respiratory reasons	Additional dose of systemic corticosteroids Prolongation of systemic corticosteroidsc > 8 d Upgrade of antibiotics*	New course of systemic corticosteroids New course of antibiotics
2. Step-up in hospital care or readmission for respiratory reasons	Transfer to the ICU	Readmission
3. All-cause mortality	—	—

Day 1 : randomization; Day X: day of discharge, at the investigator's discretion; Day 90: end of intervention.
**Change or narrowing of the initial antibiotics given as part of the standardized acute treatment during the index event (consisting of 5 d of fixed dose systemic corticosteroids and 5-7 d of antibiotics) based on proven bacterial cultures was not considered as treatment failure but as good clinical practice.*

All analyses were performed in the intention-to-treat population, and the primary endpoint was also assessed in the per-protocol population, excluding patients with one or more major protocol violations (which included a standardized acute treatment that was not respected, a concomitant use of macrolide antibiotics for more than 10 days, and unverifiable compliance with regard to study drug intake). Outcomes were analyzed using time-to-event methods. TF and mortality were analyzed by Kaplan-Meier survival analysis and compared between groups using a log-rank test. TI and SH were analyzed by a

cumulative incidence function, taking mortality as a competing risk into account, and compared between groups using Gray's test. Patients without an event within 90 days were censored at Day 90, and patients of whom the participation was terminated early were censored at the time of withdrawal. The treatment effect was estimated by the HR, obtained from a Cox regression. The treatment effects of the secondary endpoints were estimated by the difference in means using the mean cumulative function, the difference in expected means using a weighted generalized estimating equations model, and the rate ratio using a Poisson regression model, as specified in the statistical analysis plan. To control the overall type I familywise error rate of the key secondary endpoints, a serial gatekeeping method was used.

ECG data were analyzed as repeated measures of differences ($\dot{\Delta}$) compared with baseline, with Bonferroni *post hoc* correction for multiple testing. Other safety outcomes were compared between groups using a Chi-square or Fisher's exact test. All analyses were performed using SAS software version 9.4.

Results

PATIENTS

A total of 2,063 patients were screened by 15 centers within the Consortium, and 301 of these patients (15%) were randomized to azithromycin ($n = 147$) or placebo ($n = 154$). The study was completed by 118 patients in the azithromycin group (80%) and 115 in the placebo group (75%) (Figure 2). The baseline characteristics of the 301 randomized patients are summarized in Table 2. Mean study drug adherence was 95.7% and 96.2% in the azithromycin and placebo groups, respectively.

PRIMARY ENDPOINT AND COMPONENTS

Within 3 months after randomization, 69 patients in the azithromycin group and 86 in the placebo group experienced TF. TI, SH, and mortality occurred in 66 and 85, 18 and 39, and 3 and 6 patients in the azithromycin and placebo groups, respectively. The unadjusted TF rate within 3 months was 49% in the azithromycin group and 60% in the placebo group (HR, 0.73; 95% confidence interval [CI], 0.53-1.01; $P = 0.0526$) (Figure 3). The unadjusted TI, SH, and mortality rates were 47% and 60% (HR, 0.70; 95% CI, 0.51-0.97; $P = 0.0272$), 13% and 28% (HR, 0.43; 95% CI, 0.25-0.75; $P = 0.0024$), and 2% and 4% (HR, 0.62; 95% CI, 0.15-2.59; P = 0.5075) in the azithromycin and placebo groups, respectively. The differences between treatment groups were lost 6 months after study drug withdrawal (Figure 4). Results from the per-protocol analyses were almost identical to those obtained from the intention-to-treat analyses (online supplement).

SECONDARY ENDPOINTS

The effects of azithromycin on the secondary endpoints are summarized in Table 3. Within 3 months after randomization, the mean cumulative number of TFs (first key hierarchical secondary endpoint) was reduced in the azithromycin group as compared with the placebo group (Δ= -0.24; 95% CI, -0.48 to 0.00; $P = 0.0395$). No significant differences were found in quality of life (European Quality of Life-5 Dimensions [EQ5D] questionnaire) or symptom assessment scores (CAT, modified Medical Research Council [mMRC], and SSQ5 questionnaires). The unadjusted rate of new exacerbations (defined as the composite of a new course of systemic corticosteroids and/or antibiotics, or hospitalization for respiratory reasons, all after the index event) within 3 months was reduced in the azithromycin group compared with the placebo group (HR, 0.70; 95% CI, 0.49-1.00; P = 0.0497). Within 3 months after

randomization, the total hospital and ICU days were reduced (rate ratio, 0.76; 95% CI, 0.63-0.92; $P = 0.0061$; and rate ratio, 0.26; 95% CI, 0.15-0.47; $P < 0.0001$, respectively). Notably, the latter remained reduced 6 months after study drug withdrawal ($P<0.0001$). Furthermore, the total dose of systemic corticosteroid use and total days of nonstudy antibiotic use were respectively higher (rate ratio, 1.06; 95% CI, 1.04-1.08; P< 0.0001) and lower (rate ratio, 0.77; 95% CI, 0.68-0.86; P< 0.0001) in the azithromycin group than in the placebo group. No significant group differences were found in prebronchodilator FEV1 or number of general practitioner visits.

Upon hospital discharge, the COPD inhaled maintenance therapy in both groups was adjusted compared with hospital admission with a step-up to triple therapy (a combination of inhaled corticosteroids [ICS], long-acting muscarinic antagonists, and long-acting β-agonists [LABA]) and step-down in ICS/LABA. Three months after randomization, a slightly greater percentage of azithromycin-treated patients received triple therapy as compared with the placebo group (80.9% vs. 71.3%); however, no significant difference in the distribution of concurrent inhaled maintenance therapy was found (online supplement).

SUBGROUP ANALYSES

Eight subgroups were assessed for the primary and key secondary endpoints. We found no statistically significant interaction between the intervention and any of the subgroups (online supplement).

Figure 2. *Enrollment, allocation, follow-up, and analysis of the trial participants, exclusion based on one or more of the exclusion criteria, with the exception of a prolonged QTcB, chronic azithromycin intake, and a noninfectious AECOPD. *Exclusion based on criteria limiting the ability of the patient to participate in the study (e.g., comorbidities, social circumstances, etc.). Day 90: end of intervention; Day 270: end of follow-up. AECOPD = acute exacerbation of chronic obstructive pulmonary disease; (S)AE = (serious) adverse event; QTcB = QT interval corrected according to Bazett's formula.*

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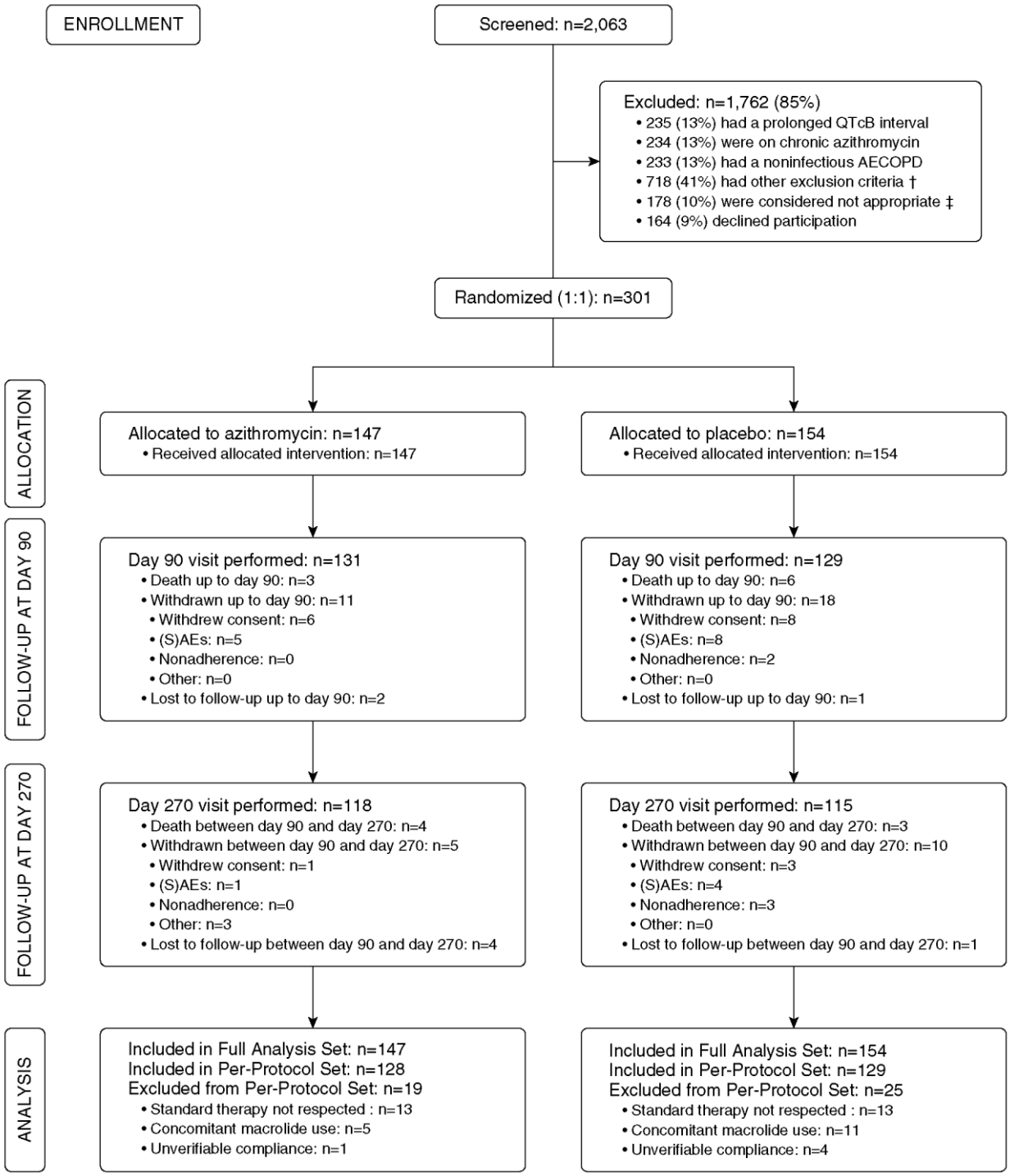

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Table 2. *Baseline Characteristics of the Subjects*

	Azithromycin ***(n= 147)***	**Placebo** ***(n = 154)***
Demographics		
Age, yr	66 ±9	67 ±10
Female sex, no. (%)	66 (45)	66 (43)
Weight, kg	67 ±20	70 ±18
Height, m	1.66 ± 9	1.66 ± 9
Body mass index, kg/m^2	24.5 ±5.9	25.1 ±6.5
Comorbidity		
Charlson comorbidity index	4 (3-5)	4 (3-5)
COPD comorbidity index	1 (0-2)	1 (1-2)
Lung disease		
mMRC dyspnea score	4(2-4)	4(2-4)
Prebronchodilator FEV_1, L	0.90 (0.69-1.23)	0.95(0.71-1.36)
Prebronchodilator FEV_1% predicted	36.0 (26.3-53.8)	38.5 (29.0-52.0)
Prebronchodilator FVC, L	2.26 (1.77-3.19)	2.24(1.80-2.89)
Prebronchodilator FVC% predicted	73.0 (58.3-93.8)	71.5(56.3-88.8)
Prebronchodilator FEV_1,/FVC, %	40.3 (33.6-8.0)	45.0 (37.0-52.8)
GOLD stage, no. (%)*		
A	0 (0)	1 (1)
B	26 (18)	30 (20)
C	1 (1)	2(1)
D	120 (82)	121 (79)
Current smoker, no. (%)	63 (43)	65 (42)
Smoking history, pack-years	44 (37-50)	43 (35-50)
Number of AECOPDs in previous year, no. (%)		
1	38 (26)	51 (33)
2	41 (28)	37 (24)
3	31 (21)	19(12)
>3	37 (25)	47 (31)
Of which number of hospitalizations due to an AECOPD, no. (%)		
0	64 (44)	64 (42)
1	55 (37)	58 (38)
2	15 (10)	16 (10)
3	6 (4)	6(4)
>3	7(5)	10(6)
Inhaled therapy for COPD, no. (%)		
LABA	136 (93)	145(94)
LAMA	118 (80)	123(80)
Inhaled corticosteroids	118(80)	123(80)
SABA	108 (73)	109(71)
Admission presentation		
Lower respiratory symptoms, no. (%)		
Cough	115 (78)	108(70)
Sputum production	97 (66)	86 (56)
Sputum purulence	67 (46)	57 (37)
GP intervention before admission		

Systemic corticosteroids	48 (33)	37 (24)
Antibiotics	50 (34)	54 (35)
Laboratory		
C-reactive protein, mg/L	14.2 (3.5-61.4)	21.6(4.5-59.6)
Leukocytes, $X10^9$/L	10.95 (9.00-13.89)	9.90 (8.20-13.70)
Neutrophils, $X10^9$/L	8.20 (6.00-11.20)	7.70(5.60-11.20)
Eosinophils, $X10^9$/L	0.06 (0.00-0.20)	0.07 (0.00-0.20)
Standardized acute treatment		
Respected, no. (%)	134 (91)	141 (92)
Received antibiotic, no. (%)	145 (99)	152 (99)
Antibiotic group, no. (%)		
β-lactam antibiotics	91 (62)	87 (57)
Quinolone antibiotics	61 (42)	71 (46)
Clindamycin	1 (1)	1 (1)
Macrolides	2(1)	4(3)
Pathogen susceptible to antibiotic, no. (%)†	136 (94)	144(95)

Definition of abbreviations: AECOPD = acute exacerbation of chronic obstructive pulmonary disease; COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease, guideline 2017; GP = general practitioner; LABA = long-acting β-agonist; LAMA = long-acting muscarinic antagonist; mMRC = modified Medical Research Council questionnaire; SABA = short-acting β-agonist.
Data are presented as no. (%), mean ± SD, and median (interquartile range).
**GOLD stages are not taking the current hospital admission into consideration.*
†Susceptibility was determined based on the need for antibiotic upgrade before discharge. Change or narrowing of the initial antibiotic based on proven bacterial cultures was considered good clinical practice.

SAFETY OUTCOMES

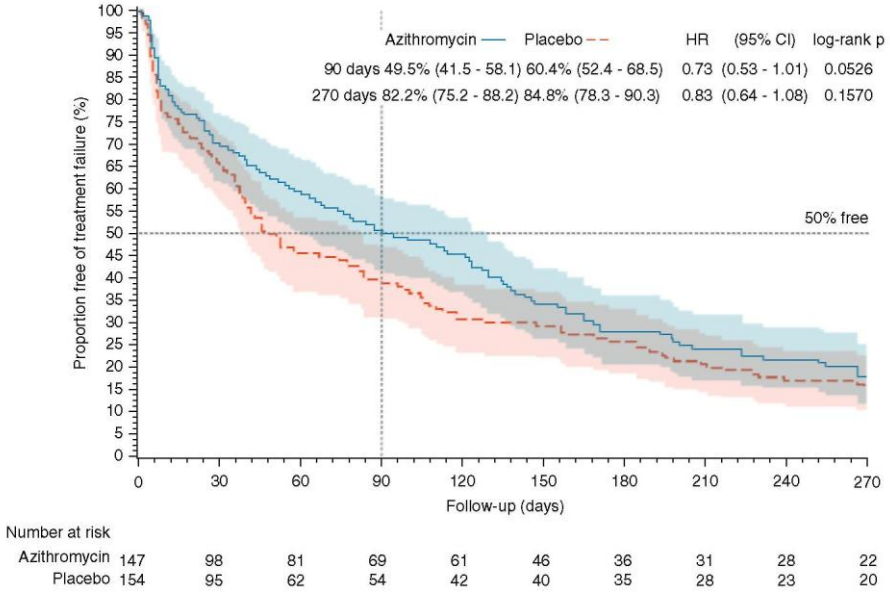
All-cause mortality at 3 months was 2% in the azithromycin group and 4% in the placebo group (P = 0.5023). Mortality from respiratory and cardiovascular causes at 3 months was 0% and 2% *(P* = 0.2479) and 2% and 1% *(P* = 0.6783) in the azithromycin and placebo groups, respectively. No significant differences were observed in the frequency of serious adverse events or adverse events leading to study drug discontinuation. Reported gastrointestinal adverse events occurred more frequently during the treatment period as compared with the follow-up period, however, no significant group differences were found (online supplement).

A total of 228 patients (114 [50%] receiving azithromycin) had all four ECGs available. Heart rate at baseline was significantly higher compared with the other time points (*P*< 0.001), with no difference between treatment groups *(P* = 0.552). At baseline, the overall mean QTcB was 427.4 ±21.6 ms, and the overall mean QTcF was 400.8 ±21.3 ms (Δ = -26.6 ± 12.8 ms; *P* < 0.001). Overall, no significant QTc prolongation was observed in the azithromycin group (online supplement) with either QTcB or QTcF. The study medication was stopped due to prolongation of the QTcB interval >500 ms or ΔQTcB > 60 ms in three patients (1%; two in the azithromycin group at Day 4, and one in the placebo group at Day X + 28). However, when using QTcF, two of these patients no longer had significant QTc prolongation, and only for one patient (receiving azithromycin) did the decision to discontinue the study remain valid. No patients developed a clinically serious arrhythmia.

Bacterial cultures on spontaneous sputum samples were obtained in 74% of the azithromycin group and 67% of the placebo group at baseline, and in 37% and 41% at Day X, 12% and 17% at Day 90, and 17% and 13% at Day 270, respectively. At baseline, the most commonly cultured bacteria were *Haemophilus influenzae* (11%), *Streptococcus pneumoniae* (9%), *Pseudomonas aeruginosa* (4%), *Moraxella catarrhalis*

(4%), and *Staphylococcus aureus* (2%). Although no significant differences were observed in the proportion of macrolide-sensitive and macrolide-resistant bacteria, a significant group difference at baseline was found for *Haemophilus influenzae* (16.5% in the azithromycin group vs. 4.9% in the placebo group; $P = 0.006$). During follow-up, no significant group differences were found for positive sputum cultures with newly acquired pathogens, or for the acquisition of macrolide-resistant bacteria (online supplement).

Figure 3. *Primary composite endpoint, treatment failure rate. The figure shows the percentage of patients who were free from treatment failure during 9 months (or 270 d) of follow-up after randomization, according to study group. Participants who did not have an event within 270 days or were terminated early were censored at Day 270 and the time of termination, respectively. CI = confidence interval; HR = hazard ratio.*

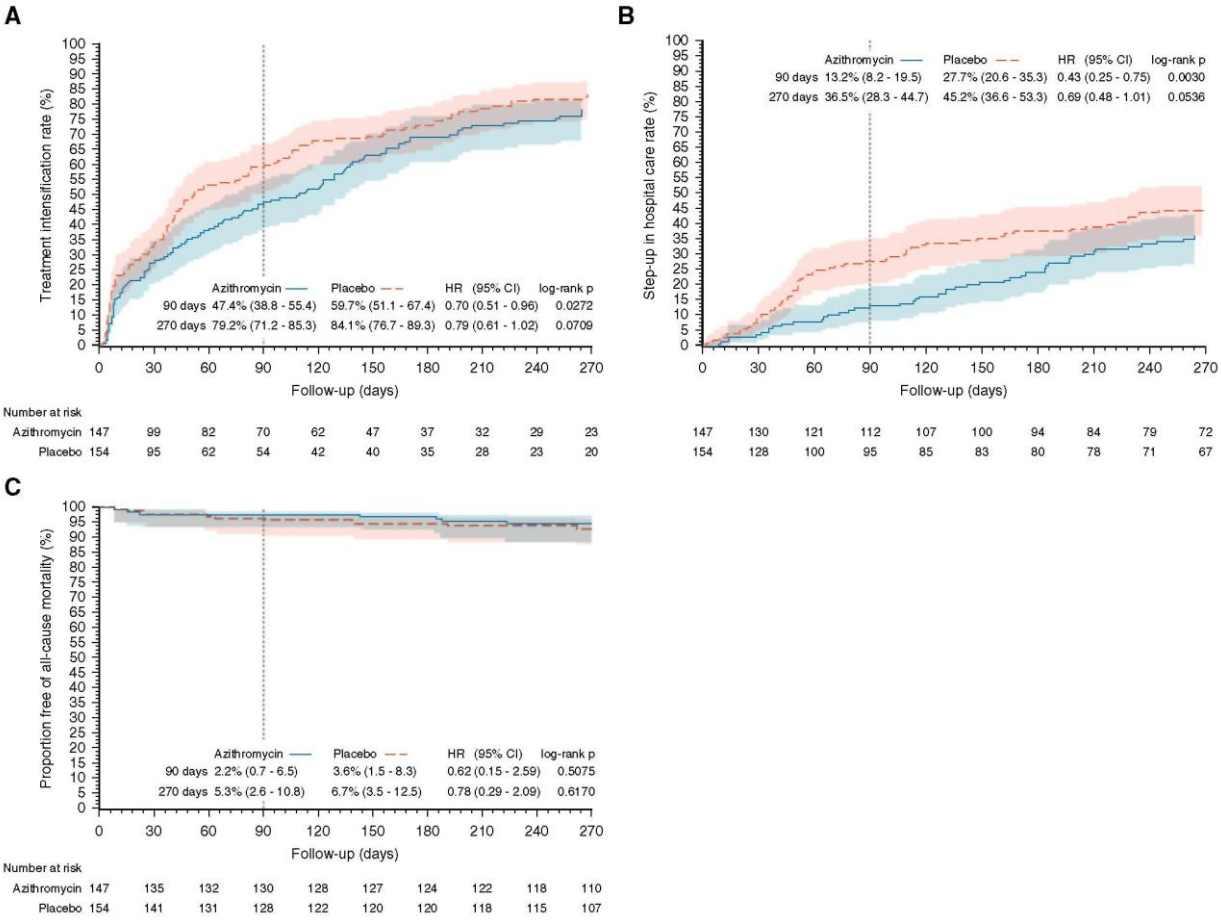


Discussion

The BACE trial (Belgian Trial with Azithromycin for Acute COPD Exacerbations Requiring Hospitalization) is the first trial to evaluate macrolide treatment as an acute intervention for patients hospitalized for a severe AECOPD. In this trial, the 18% reduction in the TF rate within 3 months after hospital admission in the azithromycin group compared with the placebo group did not meet the predetermined level of statistical significance ($P = 0.0526$), as the trial was underpowered due to early termination for slow recruitment. Although the results are formally negative, there is a strong trend in favor of the 3-month intervention with low-dose azithromycin significantly reducing the number of TFs, as well as the rates of TI and SH for respiratory reasons (by more than 20% and 50%, respectively). Although methodological heterogeneity prevents a direct comparison of results, the observed risk reduction in the rate of new exacerbations (30%) was similar in magnitude to that reported in other long-term macrolide studies in COPD (7, 18). We documented a 57% risk reduction for SH (consisting of transfer to the ICU during the index event and readmission for a new exacerbation after discharge) over a 3-month period. This effect translated to a 24% and 74% reduction in total hospital and ICU days, respectively, with the latter remaining significantly reduced 6 months after azithromycin withdrawal. Preventing COPD readmissions

after an exacerbation is an international priority aimed at slowing down disease progression and limit healthcare costs (6, 19). Apart from the recently published IMPACT (Informing the Pathway of COPD Treatment) trial, which showed a 34% reduction in hospital admissions with ICS (20), and the REACT (Roflumilast and Exacerbations in Patients Receiving Appropriate Combination Therapy) trial, which showed a 24% reduction with phosphodiesterase-4 inhibitors (21), no other evidence-based chronic intervention has demonstrated such a large potential on top of maintenance therapy with long-acting bronchodilators (22).

Figure 4. *The three components of treatment failure. (A-C) Percentage of patients who required treatment intensification for respiratory reasons (A), required a step-up in hospital care for respiratory reasons (B), and were free from mortality (C) during 9 months (or 270 d) of follow-up after randomization, according to study group. Participants who did not have an event within 270 days or were terminated early were censored at Day 270 and the time of termination, respectively. CI = confidence interval; HR = hazard ratio.*



Moreover, acute interventions that are initiated for a severe AECOPD are mostly restricted to the hospitalization period and are often completed before full clinical resolution is achieved. Consequently, they may leave an active inflammatory process smoldering at the time of discharge and render the patient vulnerable to relapse (23, 24). By providing a cross-continuum between the acute treatment phase in the hospital and ambulatory therapeutic prolongation for 3 months, our proposed intervention may help to address the highest-risk period for readmission and provide a new treatment strategy for a severe infectious AECOPD requiring hospitalization. Future *post hoc* analyses are needed to elucidate the

underlying mechanism by assessing the added value of positioning azithromycin in the acute setting (potentially maximizing both antimicrobial and antiinflammatory effects) in addition to a limited prolonged administration to prevent relapse. Intriguingly, the total number of days of antibiotic use was significantly decreased by the intervention, whereas the total dose of systemic corticosteroids was increased. This might indicate a shift in the type of exacerbations experienced by patients receiving azithromycin therapy, which could also be observed in the COLUMBUS (COPD: Influence of Macrolides on Exacerbation Frequency in Patients) trial data (9). Although bacterial infections and exacerbations might be prevented by azithromycin therapy (25, 26), patients receiving azithromycin remain prone to exacerbations of a different etiology, which may be more refractory to standard care and require a higher dose of systemic corticosteroids (27, 28). This may also explain why no statistically significant differences were found in quality of life or symptom assessment scores, as assessed by the EQ5D, CAT, and mMRC questionnaires

The BACE trial is also the first to explore azithromycin withdrawal after a prolonged course in high-risk patients with COPD. The time-to-event curves of TF and TI appear to diverge up to 1 month after azithromycin withdrawal and even 3 months for SH. This observation is supported by the molecule's prominent pharmacokinetic features, i.e., a long half-life and high lung tissue concentrations after repeated administration (29). Although these findings support the BACE trial's rationale for dose and treatment duration to establish and maintain therapeutic benefits, they may not exclude the possibility that a maximal effect was not yet reached under the proposed 3-month duration and a reduced dosage of 250 mg of azithromycin every other day. The clear convergence of the time-to-event curves 6 months after study drug withdrawal demonstrates that prolonged treatment with azithromycin appears to be necessary to sustain its clinical benefits. This argues against our hypothesis that prolonged treatment for 3 months might sufficiently interrupt the vicious circle of inflammation to alter the phenotype of "frequent exacerbator." Caution in the use of intermittent treatment courses of azithromycin is therefore warranted.

The intervention was well tolerated, with no significant differences in the frequency of (serious) adverse events. Gastrointestinal symptoms were most often reported and results were comparable to those observed in long-term studies (30). Significant QTc prolongation necessitating study drug discontinuation was rare, particularly when patients with a prolonged QTc were excluded before treatment. A prolonged QTcB at admission excluded 13% of the screened population, and ECG monitoring led to treatment interruption in only two patients treated with azithromycin, supporting earlier findings (31). The use of QTcF could minimize false-positive cases (16) and better justify patient access to azithromycin therapy without impairing safety. The main risk of chronic use of azithromycin is the induction of bacterial resistance (11, 32). In a trial by Albert and colleagues, 81% of colonizing pathogens in the azithromycin group were resistant to macrolides, as compared with 41% in the placebo group (7). A related concern is the wider spread of macrolide resistance to the general population and the potential risk of losing azithromycin as part of the first-line treatment for nontuberculous mycobacterial infections (33, 34). Macrolide resistance was monitored; however, as induced sputum was not required per protocol, the limited number of spontaneous sputum samples did not allow for a thorough evaluation of antibiotic resistance induced by azithromycin on top of a standardized acute treatment of systemic corticosteroid and antibiotics in the acute setting.

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Table 3. *Primary, Key Hierarchical, and Other Secondary Endpoints in the Intention-to-Treat Population*

	Visit	Azithromycin (*n = 147*)	Placebo (*n = 154*)	Estimator	Treatment Effect (95% CI)	*P* Value
Primary endpoint						
Treatment failure rate*	Day 90	49.5(41.5 to 58.1)	60.4(52.4 to 68.5)	HR	0.73(0.53 to 1.01)	0.0526
Key hierarchical secondary endpoints						
Number of treatment failures†	Day 90	0.79(0.62 to 0.95)	1.03(0.85 to 1.20)	Δ in MCF	-0.24(-0.48 to 0.00)	0.0395
CAT score‡	Day 90	17.7(16.4 to 19.0)	16.9(15.5 to 18.3)	Δ in means	0.35(-1.43 to 2.13)	0.6970
Total days of steroid use§	Day 90	15.9(14.9 to 16.9)	14.8(13.9 to 15.7)	Rate ratio	1.07(0.98 to 1.17)	0.1217
Other secondary endpoints						
Treatment failure rate*	Day 270	82.2(75.2 to 88.2)	84.8(78.3 to 90.3)	HR	0.83(0.64 to 1.08)	0.1570
Number of treatment failures†	Day 270	2.41(2.08 to 2.73)	2.54(2.21 to 2.87)	Δ in MCF	-0.13(-0.60 to 0.34)	0.1103
CAT score‡	Day 270	18.3(16.8 to 19.8)	18.5(17.0 to 20.0)	Δ in means	-0.87(-2.85 to 1.12)	0.3921
Total days of steroid use§	Day 270	27.1(26.1 to 28.2)	27.2(26.2 to 28.3)	Rate ratio	1.00(0.94 to 1.05)	0.8817
Treatment intensification rate‖	Day 90	47.4(38.8 to 55.4)	59.7(51.1 to 67.4)	HR	0.70(0.51 to 0.96)	0.0272
	Day 270	79.2(71.2 to 85.3)	84.1(76.7 to 89.4)	HR	0.79(0.61 to 1.02)	0.0709
Step-up in hospital care rate‖	Day 90	13.2(8.2 to 19.5)	27.7(20.6 to 35.3)	HR	0.43(0.25 to 0.75)	0.0030
	Day 270	36.5(28.3 to 44.7)	45.2(36.6 to 53.3)	HR	0.69(0.48 to 1.01)	0.0536
Mortality rate*	Day 90	2.2(0.7 to 6.5)	3.6(1.5 to 8.3)	HR	0.62(0.15 to 2.59)	0.5075
	Day 270	5.3(2.6 to 10.8)	6.7(3.5 to 12.5)	HR	0.78(0.29 to 2.09)	0.6170
New exacerbation rate‖	Day 90	39.6(31.3 to 47.7)	51.0(42.3 to 59.0)	HR	0.70(0.49 to 1.00)	0.0497
	Day 270	75.1(66.6 to 81.7)	79.5(71.5 to 85.5)	HR	0.81(0.62 to 1.06)	0.1324
Number of new exacerbations†	Day 90	0.57(0.44 to 0.70)	0.75(0.60 to 0.90)	Δ in MCF	-0.18(-0.37 to 0.02)	0.0770
	Day 270	2.08(1.80 to 2.36)	2.18(1.92 to 2.45)	Δ in MCF	-0.10(-0.49 to 0.28)	0.5997
Total dose of steroid use (mg)§	Day 90	340.2(335.4 to 345.1)	321.8(317.6 to 326.0)	Rate ratio	1.06(1.04 to 1.08)	<0.0001
	Day 270	603.4(598.4 to 608.5)	603.5(598.4 to 608.6)	Rate ratio	1.00(0.99 to 1.01)	0.9903
Total days of nonstudy antibiotics§	Day 90	10.5(9.6 to 11.5)	13.7(12.8 to 14.7)	Rate ratio	0.77(0.68 to 0.86)	<0.0001
	Day 270	21.1(20.2 to 22.1)	21.6(20.7 to 22.6)	Rate ratio	0.98(0.92 to 1.04)	0.4592

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Total hospital days§	Day 90	10.7(9.3 to 12.3)	14.0(12.3 to 16.1)	Rate ratio	0.76(0.63 to 0.92)	0.0061
	Day 270	22.2(18.3 to 27.0)	28.5(23.8 to 34.2)	Rate ratio	0.78(0.60 to 1.01)	0.0631
Total ICU days§	Day 90	3.0(1.8 to 5.1)	11.4(9.1 to 14.3)	Rate ratio	0.26(0.15 to 0.47)	<0.0001
	Day 270	5.1(4.0 to 6.5)	11.1(9.2 to 13.3)	Rate ratio	0.46(0.34 to 0.63)	<0.0001
Number of GP contacts§	Day 90	2.4(2.0 to 2.7)	2.6(2.3 to 3.0)	Rate ratio	0.90(0.74 to 1.10)	0.3119
	Day 270	6.1(5.7 to 6.6)	6.6(6.1 to 7.1)	Rate ratio	0.92(0.83 to 1.03)	0.1511
Prebronchodilator FEV_1 (L)‡	Day 90	1.3(0.9 to 1.7)	1.2(1.1 to 1.3)	Δ in means	0.13(-0.26 to 0.53)	0.5008
	Day 270	1.1(1.0 to 1.2)	1.2(1.1 to 1.3)	Δ in means	-0.09(-0.23 to 0.05)	0.1933
mMRC score‡	Day 90	3.1(3.0 to 3.3)	3.2(3.0 to 3.4)	Δ in means	-0.08(-0.33 to 0.17)	0.5389
	Day 270	3.3(3.2 to 3.5)	3.2(3.0 to 3.4)	Δ in means	0.08(-0.20 to 0.35)	0.5886
EQ5D score‡	Day 90	61.6(58.3 to 65.0)	61.2(57.7 to 64.6)	Δ in means	0.34(-4.28 to 4.97)	0.8842
	Day 270	57.3(53.7 to 60.9)	60.2(56.3 to 64.1)	Δ in means	-2.73(-7.86 to 2.40)	0.2967
SSQ5 score‡	Day 90	8.1(7.8 to 8.4)	7.9(7.6 to 8.2)	Δ in means	0.18(-0.13 to 0.49)	0.2559
	Day 270	8.2(7.8 to 8.5)	8.0(7.7 to 8.3)	Δ in means	0.20(-0.12 to 0.52)	0.2140

Definition of abbreviations: CAT = COPD assessment test; CI = confidence interval; COPD = chronic obstructive pulmonary disease; Δ = symbol indicating difference; GP = general practitioner; HR = hazard ratio; MCF = mean cumulative function; mMRC = modified Medical Research Council questionnaire; EQ5D = European Quality of Life-5 dimensions questionnaire; SSQ5 =Speech, Spatial, and Qualities of Hearing Scale-5 items questionnaire.
Day 90: end of intervention; Day 270: end of follow-up.
**Event rate (95% CI) obtained using Kaplan-Meier methodology. Groups were compared using a log-rank test. Treatment effect presented as HR.*
† MCF (95% CI). Groups were compared using a log-rank test for MCFs. Treatment effect is presented as the difference in MCF.
‡ Estimated mean value (95% CI) obtained using a weighted general estimating equations model with factors for group and treatment, and their interaction. Baseline was included as a
covariate. Groups were compared using general estimating equations by a Chi-squared test. Treatment effect presented as difference in expected means.
§ Analyzed using a Poisson regression model. The natural logarithm of the total number of days up to the visit day was used as offset. Treatment effect is presented as the rate ratio.
‖ Cumulative incidence function (95% CI), using overall mortality as the competing risk. Groups were compared using Gray's test. Treatment effect is presented as the HR. A new exacerbation is defined as the composite of treatment intensification and step-up in hospital care for respiratory reasons after the index event.

In analogy to major adverse cardiovascular events (MACE), a commonly used composite endpoint for cardiovascular research (35), the BACE trial provides the first results on a composite endpoint to evaluate interventions during an AECOPD requiring hospitalization. In addition to reducing the required sample size in a difficult setting, the use of TF allowed for the evaluation of in-hospital outcomes, as well as the relapse rate during 3 months after discharge. Although TI during hospital admission is often neglected, it may capture important differences in the resolution of the index event. Because we defined TI in a continuum of 3 months, it also incorporated transfer to the ICU, readmission, and new exacerbations, as these events are unavoidably associated and often preceded with new courses of systemic corticosteroids and/or antibiotics. In fact, TI covered 96% and 99% of the total event rate of TF over 3 months in the azithromycin and placebo groups, respectively. Future studies in this setting may therefore consider TI, which includes prolongation, up-titration, or new courses of medication as a major single endpoint.

By reducing the dose and treatment duration, and by restricting the intervention to subgroups of patients with the most unmet needs, one can obtain a more favorable benefit/risk ratio for azithromycin interventions. The potential for a significant and clinically relevant reduction in total hospital and ICU days within 3 months of hospital admission merits further investigation in large, real-life, pragmatic RCTs to validate the important health economic impact of prolonged low-dose treatment in such high-risk groups.

The BACE trial had several limitations. First, target enrollment was not met, due to a high screen failure rate (85.4%), as well as various nonscientific and funding challenges associated with investigator-initiated clinical research, which left the trial underpowered. Second, due to the low inclusion rate (14.6%) the obtained results are limited in their external validity and generalizability to other populations of patients with COPD. In particular, the findings do not support extrapolation to noninfectious exacerbations. Third, the 48-hour screening period to assess the infectious nature of the index AECOPD resulted in the inclusion of AECOPDs of viral and bacterial etiologies. Although viral AECOPDs can facilitate subsequent bacterial infections (36), procalcitonin measurements might have provided guidance as to which events would have required antibiotics as part of the standardized acute treatment (37, 38). Because most interaction tests performed in the subgroup analyses were not significant, these findings provide no insight into which type of infectious exacerbation (viral or bacterial) would benefit most from the intervention. Fourth, although all TFs were carefully adjudicated by the blinded study team, judgment regarding the necessity of TI is subjective and was left to the physician who was caring for the patient. This might have introduced between-site inhomogeneity. Fifth, although the patients were actively asked about hearing loss and questionnaires were regularly completed, no standard audiometry was performed. Finally, spontaneous sputum samples were obtained from less than 20% of the patients in both groups at Days 90 and 270, so no conclusions can be made regarding shifts in bacterial resistance.

Conclusions

In patients with COPD who have been hospitalized for a severe exacerbation, treatment with low-dose azithromycin upon admission and for 3 months thereafter (the highest-risk period for deterioration, relapse, and death) may effectively and safely reduce TF (i.e., TI and SH). Prolonged treatment, however, appears to be needed to sustain clinical benefits. A careful and individualized approach to the selection of patients with regard to proarrhythmic effects and the development of antibiotic resistance would be recommended.

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References

1. Hartl S, Lopez-Campos JL, Pozo-Rodriguez F, Castro-Acosta A, Studnicka M, Kaiser B, *et al.* Risk of death and readmission of hospital-admitted COPD exacerbations: European COPD audit. *Eur Respir J* 2016;47:113-121.

2. Hoogendoorn M, Hoogenveen RT, Rutten-van Mölken MP, Vestbo J, Feenstra TL. Case fatality of COPD exacerbations: a meta-analysis and statistical modelling approach. *Eur Respir J* 2011; 37:508-515.

3. Lodewijckx C, Sermeus W, Vanhaecht K, Panella M, Deneckere S, Leigheb F, *et al.* Inhospital management of COPD exacerbations: a systematic review of the literature with regard to adherence to international guidelines. *J Eval Clin Pract* 2009;15:1101-1110.

4. Chow L, Parulekar AD, Hanania NA. Hospital management of acute exacerbations of chronic obstructive pulmonary disease. *J Hosp Med* 2015;10:328-339.

5. Soo Hoo GW, Esquinas AM. Risk trajectories of readmission and death in the first year after hospitalization for chronic obstructive pulmonary disease: don't shortchange noninvasive ventilation. *Am J Respir Crit Care Med* 2018;198:282-283.

6. Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD).Global strategy for the diagnosis, management, and prevention of COPD, 2018 report [Internet]; 2018 [accessed 2018 Sept 30]. Available from: http://goldcopd.org.

7. Albert RK, Connett J, Bailey WC, Casaburi R, Cooper JA Jr, Criner GJ, *et al.;* COPD Clinical Research Network. Azithromycin for prevention of exacerbations of COPD. *N Engl J Med* 2011 ;365: 689-698.

8. Ni W, Shao X, Cai X, Wei C, Cui J, Wang R, *et al.* Prophylactic use of macrolide antibiotics for the prevention of chronic obstructive pulmonary disease exacerbation: a meta-analysis. *PLoS One* 2015;10: e0121257.

9. Uzun S, Djamin RS, Kluytmans JAJW, Mulder PG, van't Veer NE, Ermens AA, *et al.* Azithromycin maintenance treatment in patients with frequent exacerbations of chronic obstructive pulmonary disease (COLUMBUS): a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2014;2:361 -368.

10. Li H, Liu DH, Chen LL, Zhao Q, Yu YZ, Ding JJ, *et al.* Meta-analysis of the adverse effects of long-term azithromycin use in patients with chronic lung diseases. *Antimicrob Agents Chemother* 2014;58: 511-517.

11. Serisier DJ. Risks of population antimicrobial resistance associated with chronic macrolide use for inflammatory airway diseases. *Lancet Respir Med* 2013;1:262-274.

12. FDA Drug Safety Communication: azithromycin (Zithromax or Zmax) and the risk of potentially fatal heart rhythms (safety announcement 3-12-2013). U.S. Food and Drug Aministration [Internet] [accessed 2018 Sept 30]. Available from: https://www.fda.gov/downloads/ Drugs/DrugSafety/UCM343347.pdf.

13. Wallace MR, Miller LK, Nguyen MT, Shields AR. Ototoxicity with azithromycin. *Lancet* 1994;343:241.

14. Vermeersch K, Gabrovska M, Aumann J, Demedts IK, Corhay J-L, Marchand E, *et al.* Late breaking abstract - azithromycin for acute COPD exacerbations requiring hospitalization - the BACE trial results. *Eur Resp J* 2018;52(Suppl 62):OA1654.

15. Vermeersch K, Gabrovska M, Deslypere G, Demedts IK, Slabbynck H, Aumann J, *et al.* The Belgian trial with azithromycin for acute COPD exacerbations requiring hospitalization: an investigator-initiated study protocol for a multicenter, randomized, double-blind, placebo-controlled trial. *Int J Chron Obstruct Pulmon Dis* 2016;11 : 687-696.

16. Vandenberk B, Vandael E, Robyns T, Vandenberghe J, Garweg C, Foulon V, *et al.* Which QT correction formulae to use for QT monitoring? *J Am Heart Assoc* 2016;5:1-10.

17. Demeester K, Topsakal V, Hendrickx J J, Fransen E, van Laer L, Van Camp G, *et al.* Hearing disability measured by the speech, spatial, and qualities of hearing scale in clinically normal-hearing and hearing-impaired middle-aged persons, and disability screening by means of a reduced SSQ (the SSQ5). *Ear Hear* 2012; 33:615-616.

18. Seemungal TAR, Wilkinson TMA, Hurst JR, Perera WR, Sapsford RJ, Wedzicha JA. Long-term erythromycin therapy is associated with decreased chronic obstructive pulmonary disease exacerbations. *Am J Respir Crit Care Med* 2008;178:1139-1147.

19. KhakbanA, Sin DD, FitzGerald JM, McManus BM, Ng R, Hollander Z, *et al.* The projected epidemic of chronic obstructive pulmonary disease hospitalizations over the next 15 years: a population-based perspective. *Am J Respir Crit Care Med* 2017;195: 287-291.

20. Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, *et al.;* IMPACT Investigators. Once-daily single-inhaler triple versus dual therapy in patients with COPD. *N Engl J Med* 2018;378: 1671-1680.

21. Martinez FJ, Calverley PMA, Goehring UM, Brose M, Fabbri LM, Rabe KF. Effect of roflumilast on exacerbations in patients with severe chronic obstructive pulmonary disease uncontrolled by combination therapy (REACT): a multicentre randomised controlled trial. *Lancet* 2015;385:857-866.

22. Braman SS. Hospital readmissions for COPD: we can meet the challenge. *Chronic Obstr Pulm Dis* 2015;2:4-7.

23. Mantero M, Rogliani P, Di Pasquale M, Polverino E, Crisafulli E, Guerrero M, *et al.* Acute exacerbations of COPD: risk factors for failure and relapse. *Int J Chron Obstruct Pulmon Dis* 2017; 12: 2687-2693.

24. Miravitlles M, Anzueto A. Antibiotics for acute and chronic respiratory infection in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013;188:1052-1057.

25. Altenburg J, de Graaff CS, van der Werf TS, Boersma WG. Immunomodulatory effects of macrolide antibiotics—part 1 : biological mechanisms. *Respiration* 2011 ;81:67-74.

26. Altenburg J, de Graaff CS, van der Werf TS, Boersma WG. Immunomodulatory effects of macrolide antibiotics—part 2: advantages and disadvantages of long-term, low-dose macrolide therapy. *Respiration* 2011 ;81:75-87.

27. Celli BR, Barnes PJ. Exacerbations of chronic obstructive pulmonary disease. *Eur Respir J* 2007;29:1224-1238.

28. Papi A, Bellettato CM, Braccioni F, Romagnoli M, Casolari P, Caramori G, *et al.* Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. *Am J Respir Crit Care Med* 2006;173:1114-1121.

29. Lode H. The pharmacokinetics of azithromycin and their clinical significance. *Eur J Clin Microbiol Infect Dis* 1991 ;10: 807-812.

30. Brown BA, Griffith DE, Girard W, Levin J, Wallace RJ Jr. Relationship of adverse events to serum drug levels in patients receiving high-dose azithromycin for mycobacterial lung disease. *Clin Infect Dis* 1997;24: 958-964.

31. Albert RK, Schuller JL; COPD Clinical Research Network. Macrolide antibiotics and the risk of cardiac arrhythmias. *Am J Respir Crit Care Med* 2014;189:1173-1180.

32. Malhotra-Kumar S, Lammens C, Coenen S, Van Herck K, Goossens H. Effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers: a randomised, double-blind, placebo-controlled study. *Lancet* 2007; 369:482-490.

33. Wenzel RP, Fowler AA III, Edmond MB. Antibiotic prevention of acute exacerbations of COPD. *N Engl J Med* 2012;367: 340-347.

34. Desai H, Richter S, Doern G, Heilmann K, Dohrn C, Johnson A, *et al.* Antibiotic resistance in sputum isolates of Streptococcus pneumoniae in chronic obstructive pulmonary disease is related to antibiotic exposure. *COPD* 2010;7:337-344.

35. Lim E, Brown A, Helmy A, Mussa S, Altman DG. Composite outcomes in cardiovascular research: a survey of randomized trials. *Ann Intern Med* 2008;149:612-617.

36. Molyneaux PL, Mallia P, Cox MJ, Footitt J, Willis-Owen SA, Homola D, *et al.* Outgrowth of the bacterial airway microbiome after rhinovirus exacerbation of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013;188:1224-1231.

37. Lin C, Pang Q. Meta-analysis and systematic review of procalcitonin- guided treatment in acute exacerbation of chronic obstructive pulmonary disease. *Clin Respir J* 2018;12:10-15.

38. Corti C, Fally M, Fabricius-Bjerre A, Mortensen K, Jensen BN, Andreassen HF, *et al.* Point-of-care procalcitonin test to reduce antibiotic exposure in patients hospitalized with acute exacerbation of COPD. *Int J Chron Obstruct Pulmon Dis* 2016;11:1381-1389.