Antibiotic treatment and factors influencing short and long-term outcomes of acute exacerbations of chronic bronchitis

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ABSTRACT

Background: The MOSAIC study compared moxifloxacin to 3 standard antibiotic regimens in Anthonisen type 1 acute exacerbations of chronic bronchitis (AECB). Further exploratory analyses were performed to identify prognostic factors of short and long term clinical outcomes, and their value for clinical research.

Methods: Outpatients $\geq 45$ years were screened between AECB episodes, randomized to treatment upon presenting with an AECB, assessed 7-10 days after study treatment, and followed monthly until a new AECB or up to 9 months. Logistic regression assessed the predictive factors for clinical cure (return to pre-AECB status) and clinical success (cure or improvement), and a stepwise Cox regression model time to a composite event (failure of study treatment, new AECB, or further antibiotic treatment for AECB).

Results: In multivariate analyses, clinical cure was positively influenced by treatment with moxifloxacin (Odds Ratio=1.49; 95% CI: 1.08-2.04), while cardiopulmonary disease (OR=0.59; 95% CI: 0.38-0.90), FEV$_1$ $<$50% predicted (OR=0.48; 95% CI: 0.35-0.67) and $\geq$4 AECB in previous year (OR=0.68; 95% CI: 0.48-0.97) predicted poorer outcome. For clinical success, treatment with moxifloxacin had a positive influence (OR=1.57; 95% CI: 1.03-2.41), while cardiopulmonary disease (OR=0.41; 95% CI: 0.25-0.68) and use of acute bronchodilatators (OR=0.50; 95% CI: 0.30-0.84) predicted poorer outcome. The occurrence of the composite event was influenced by antibiotic treatment (Hazard Ratio=0.82; 95% CI: 0.68-0.98), age $\geq$65 years (HR=1.22; 95% CI: 1.01-1.47), FEV$_1$ $<$50% predicted (HR=1.27; 95% CI: 1.05-1.53), $\geq$4 AECB in previous year (HR=1.63; 95% CI: 1.34-1.99) and acute bronchodilator use (HR=1.48; 95% CI: 1.17-1.87). For the composite event the beneficial effect of moxifloxacin was primarily seen in patients aged $\geq$65 years.

Conclusion: Despite selection of a homogeneous population of chronic bronchitis patients between group differences relating to antibiotic treatment could still be confounded by factors related to medical history, severity of disease and use of concomitant medicators. Design of future clinical trials should take these factors into account.
Key words: exacerbation of chronic bronchitis, moxifloxacin, prognostic factor, antibiotic, treatment outcome.

INTRODUCTION

There is increasing evidence for the role of bacterial infection in causing acute exacerbations of chronic obstructive pulmonary disease (AECOPD), particularly in those patients with chronic bronchitis (CB) who present with all three cardinal symptoms defined by Anthonisen et al (1). The frequency of exacerbations adversely affects disease progression and overall health status (2-4). Studies involving sputum analysis, bronchoscopic sampling, molecular epidemiology of bacterial strains and immunology have linked the presence of bacterial infection with AECOPD and bacterial eradication with recovery (5-10). Chronic inflammation has been associated with bacterial persistence, and the number of bacteria present in the airway with disease progression (11-14).

It is therefore surprising that the benefits of antibiotic treatment of exacerbations have not been more clearly defined (15, 16). Most guidelines have used the Anthonisen criteria to decide when an antibiotic should be prescribed, but little evidence of efficacy differences between antibiotics has been gathered (1, 15). In the context of a marked increase in the prevalence of bacterial strains resistant to antibiotics such as amoxicillin, tetracycline and erythromycin, the recently published Canadian guidelines have attempted to define at risk patients who might benefit from newly developed antibiotics that are active against resistant strains (15,17, 18).

In a meta-analysis of AECOPD placebo-controlled trials, there was a small but significant benefit from antibiotic treatment on overall recovery and change in peak-flow (19). However most antibiotic trials have compared one antibiotic to another. These trials were usually evaluating a short-term outcome, defined as improvement in signs and symptoms sufficient so that further antibiotic prescription is not necessary. They compared antibiotic regimens in
heterogeneous populations, with poorly defined disease severity and most studies were underpowered to demonstrate superiority (15). In that context, they have almost all shown clinical equivalence, even when one antibiotic has shown superior bacteriological eradication (15, 20). This discrepancy could have several explanations. Most airway infections causing AECOPD are superficial, although mucosal invasion can occur, and efficient host defenses lead to high spontaneous recovery rates (1, 21). The opportunity to show differences between antibiotics may be greater in patients with more severe disease, or with risk factors for poor outcome (15, 22). Patients with persistent bacterial infection due to ineffective antibiotic treatment might improve by reducing bacterial numbers, but their recovery may be incomplete and they could have a more rapid relapse (11). Consequently, long-term follow up might reveal differences in efficacy between antibiotics.

The MOSAIC study was designed to meet those shortcomings (22). This large trial compared the short and long-term outcomes of antibiotic treatments in a population with a history of heavy smoking and significant lung function impairment. Moxifloxacin showed clinical equivalence to standard therapy for clinical success (the primary outcome measure), and achieved superior clinical cure rates, defined as return to baseline health status, and significantly higher bacteriologic eradication rates over standard therapy. Fewer patients required additional antimicrobials in the weeks following the exacerbation and the time to next AECB was significantly longer after treatment with moxifloxacin. In the analysis of a composite endpoint comprising treatment failure, new exacerbation, or any further antibiotic for lower respiratory tract illness, moxifloxacin was shown to be statistically significantly superior for up to 5 months of follow-up.

The superiority of moxifloxacin demonstrated in these secondary outcomes could be due to more successful bacteriological eradication, which led to resolution of bronchial inflammation, a complete return to baseline symptoms, fewer rapid relapses requiring antibiotic treatment, and a longer time to next exacerbation. We have now investigated which clinical features were associated with the short and long-term treatment outcomes. We have then looked at the results
of antibiotic treatments in these sub-groups to see whether the differences between moxifloxacin and comparator antibiotics were increased or reduced.

METHODS

**Design:** This was a prospective, randomized, double-blind study which design and primary outcomes were previously reported (22). Outpatients aged \( \leq 45 \) years with documented chronic bronchitis were eligible for enrolment during an AECB-free period if they had a history of cigarette smoking of at least 20 pack years, two or more documented AECB in the previous year, and \( \text{FEV}_1 \ < 85\% \) of predicted value at the enrolment visit. Patients then presenting with an Anthonisen type 1 AECB were randomized to receive either treatment with moxifloxacin (400 mg once daily for five days), or one of the following comparators chosen by the investigators between amoxicillin (500 mg three times daily for 7 days), clarithromycin (500 mg twice daily for 7 days), or cefuroxime-axetil (250 mg twice daily for 7 days).

**Endpoints:** Short term results were assessed on clinical response evaluated by the investigators 7-10 days after the end of treatment. They included clinical success defined as sufficient improvement in signs and symptoms so that the patient did not require any alternative antimicrobial therapy, and clinical cure defined as complete return to pre-exacerbation status. The long-term measurement was a composite event defined as the time to treatment failure, occurrence of a new exacerbation or any antibiotic use for a further AECB during up to nine months of follow-up.

**Factors:** The present post hoc and exploratory analyses were conducted in the intent-to-treat (ITT) population. Factors with potential impact on the clinical outcomes were selected according to literature (23-30). They were age \([<65 \ or \ \geq 65 \ years]\), body mass index \([\text{BMI} \leq 30 \ kg/m^2 \ or \ > 30 \ kg/m^2]\), sex, current smoking status, alcohol consumption, comorbidities (diabetes mellitus, coexistent cardiopulmonary disease), CB severity (number of previous AECB in the previous year \([2-3 \ or \ \geq 4]\), \( \text{FEV}_1 \ [<50\% \ vs. \ \geq50\% \ of \ predicted \ value \ at \ enrolment]\)), duration of \( \text{CB} \ (<10 \ or \ \geq 10 \ years) \), elapsed time from previous AECB \((<6 \ or \ \geq 6 \ months)\) and concomitant medications (steroid administration, bronchodilators). No steroid administration was defined as
no steroid use at randomization or no increase in long-term steroid dosage; long-term inhaled steroids administered for more than 2 months prior to randomization and/or systemic steroids started at randomization or increased dosage at randomization if previously administered were classified as steroid administration. Bronchodilator administration was defined as the use of any bronchodilator type at acute phase, i.e. between randomization and 7-10 days after end of treatment: short-acting and long-acting, beta agonist and/or anticholinergic.

**Analysis:** The association between each individual prognostic factor and clinical outcomes (clinical cure, clinical success, and composite endpoint) was tested by Chi square tests. The independent prognostic contributions of individual factors to the clinical outcomes were then tested by multivariate stepwise logistic regression analyses for clinical cure and clinical success, respectively. Because the composite endpoint was the time-dependent variable, the multivariate analysis used a stepwise Cox regression model. The threshold for statistical significance was $p=0.05$. Interactions between treatment and prognostic factors were then tested for the factors that proved significant in the multivariate analyses, using a threshold of $p=0.10$. When the interaction test was inferior to that threshold, the between-treatment difference at each level was described. The statistical software packages SAS Windows V6.12 and 8.2 were used.

**Ethics:** The study protocol was approved by ethics committees, and patients provided their written informed consent.
RESULTS

The full description of patients studied (n=730) and their randomization is given in the online supplement (Table 5). The mean age (SD) was 63.2 (9.8), 42.3% had FEV₁ <50%, 27.7% had ≥4 exacerbations in the last year and the mean (SD) years since diagnosis of chronic bronchitis was 12.5 (0.8). There was no significant difference between these values in the randomization to the two arms of the study.

Clinical cure: the factors identified in the univariate analysis were antibiotic treatment, steroid use, cardiopulmonary diseases, FEV₁, number of previous AECB and elapsed time from previous AECB. All other factors were not statistically significant (Table 1).
**Table 1**: Short-term analysis: Significant prognostic factors for clinical cure rate using univariate analysis (ITT population)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Clinical cure</th>
<th>Selected Subjects</th>
<th>Chi-2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No N=243</td>
<td>Yes N=487</td>
<td>N=730</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparator</td>
<td>140 (37%)</td>
<td>236 (63%)</td>
<td>376</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>103 (29%)</td>
<td>251 (71%)</td>
<td>354</td>
</tr>
<tr>
<td>Steroid use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>88 (28%)</td>
<td>223 (72%)</td>
<td>311</td>
</tr>
<tr>
<td>Yes</td>
<td>155 (37%)</td>
<td>264 (63%)</td>
<td>419</td>
</tr>
<tr>
<td>Cardiopulmonary disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>193 (31%)</td>
<td>432 (69%)</td>
<td>625</td>
</tr>
<tr>
<td>Yes</td>
<td>50 (48%)</td>
<td>55 (52%)</td>
<td>105</td>
</tr>
<tr>
<td>FEV1 (%) at Enrolment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 50</td>
<td>109 (26%)</td>
<td>313 (74%)</td>
<td>422</td>
</tr>
<tr>
<td>&lt; 50</td>
<td>134 (44%)</td>
<td>174 (56%)</td>
<td>308</td>
</tr>
<tr>
<td>Number of AECB in previous year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-3</td>
<td>162 (31%)</td>
<td>365 (69%)</td>
<td>527</td>
</tr>
<tr>
<td>≥4</td>
<td>81 (40%)</td>
<td>122 (60%)</td>
<td>203</td>
</tr>
<tr>
<td>Elapse time from previous AECB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 6 Months</td>
<td>122 (30%)</td>
<td>285 (70%)</td>
<td>407</td>
</tr>
<tr>
<td>≤ 6 Months</td>
<td>120 (37%)</td>
<td>201 (63%)</td>
<td>321</td>
</tr>
</tbody>
</table>

The full analysis including non significant factors is shown in the online supplement Table 6.
When a multivariate logistic model was applied, Moxifloxacin was independently associated with a higher clinical cure rate than comparator while comorbid cardiopulmonary disease, FEV$_1$ <50% predicted and $\geq 4$ AECB in the previous year had a detrimental effect on outcome (table 2).

**Table 2:** Prognostic factors associated with clinical cure rate at 7 to 10 days after the end of treatment using a stepwise logistic model (ITT population).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odd Ratio</th>
<th>Probability</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (0 : Comparator ; 1 : Moxifloxacin)</td>
<td>1.485</td>
<td>0.015</td>
<td>1.079 - 2.044</td>
</tr>
<tr>
<td>Cardiopulmonary disease (0 : No ; 1: Yes)</td>
<td>0.585</td>
<td>0.016</td>
<td>0.378 - 0.903</td>
</tr>
<tr>
<td>FEV$_1$ (%) at Enrolment (0 : $\geq 50$ ; 1 : &lt;50)</td>
<td>0.482</td>
<td>$&lt;0.001$</td>
<td>0.349 - 0.666</td>
</tr>
<tr>
<td>Number of AECB in previous year (0: 2-3; 1: $\geq 4$)</td>
<td>0.684</td>
<td>0.032</td>
<td>0.483 - 0.967</td>
</tr>
</tbody>
</table>

There was no interaction between treatment and each individual factor (cardiopulmonary: $p=0.241$; FEV$_1$ : $p=0.452$; number of AECB in previous year : $p=0.547$).

**Clinical success:** steroid use ($p=0.043$), comorbid cardiopulmonary disease ($p=0.002$), FEV$_1$ <50% predicted ($p=0.006$) and acute use of bronchodilators ($p=0.028$) were significant factors in the univariate analysis. All other factors were not significant. The full analysis is given in the online supplement Table 7. In the multivariate model, moxifloxacin was significantly superior to comparator (OR=1.573 [1.028-2.408]; $p=0.037$), while cardiopulmonary disease (OR: 0.410 [0.246-0.683]; $p<0.001$) and use of acute bronchodilators (OR =0.497 [0.296-0.835]; $p=0.008$) were detrimental independent predictive factors of outcomes. There was no interaction between treatment and each individual factor (cardiopulmonary: $p=0.274$; use of acute bronchodilators: $p=0.794$).

**Long-term outcome:** in univariate analyses, the factors that significantly impacted the occurrence of the composite event were $\geq 4$ AECB in previous year and use of acute bronchodilators use (Table 3).
Table 3: Long-term analysis: Significant prognostic factors for composite event using univariate analysis (ITT population)

<table>
<thead>
<tr>
<th></th>
<th>Composite Event</th>
<th>Selected Subjects</th>
<th>Chi-2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>N=730</td>
</tr>
<tr>
<td>Age (Years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65 Years</td>
<td>155(40%)</td>
<td>231(60%)</td>
<td>386</td>
</tr>
<tr>
<td>≥ 65 Years</td>
<td>116(34%)</td>
<td>228(71%)</td>
<td>344</td>
</tr>
<tr>
<td>P = 0.072</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of AECB in previous year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-3</td>
<td>220(42%)</td>
<td>307(58%)</td>
<td>527</td>
</tr>
<tr>
<td>≥4</td>
<td>51(25%)</td>
<td>152(75%)</td>
<td>203</td>
</tr>
<tr>
<td>P ≤ 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchodilators</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>247(40%)</td>
<td>371(60%)</td>
<td>618</td>
</tr>
<tr>
<td>Yes</td>
<td>24(21%)</td>
<td>88(79%)</td>
<td>112</td>
</tr>
<tr>
<td>P ≤ 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The full analysis including non-significant risk factors is shown in the online supplement Table 8.

In the multivariate model, antibiotic treatment, age ≥65 years, FEV₁ <50% predicted, ≥4 AECB in the previous year, and acute bronchodilator use had a statistically significant effect on long-term outcome (Table 4).
Table 4: Independent prognostic factors for occurrence of the composite event using a stepwise Cox Model (ITT population)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hazard Ratio</th>
<th>Probability</th>
<th>95% Confidence Interval Lower Limit</th>
<th>95% Confidence Interval Upper Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (0: Comparator ; 1: Moxifloxacin)</td>
<td>0.816</td>
<td>0.031</td>
<td>0.678</td>
<td>0.982</td>
</tr>
<tr>
<td>Age (0 : &lt;65 years ; 1: ≥ 65 years)</td>
<td>1.219</td>
<td>0.039</td>
<td>1.010</td>
<td>1.470</td>
</tr>
<tr>
<td>FEV$_1$ (%) at Enrolment (0 : ≥50 ; 1: &lt;50)</td>
<td>1.265</td>
<td>0.014</td>
<td>1.048</td>
<td>1.526</td>
</tr>
<tr>
<td>Number of previous AECB (0: 2-3; 1: ≥4)</td>
<td>1.631</td>
<td>&lt;0.001</td>
<td>1.338</td>
<td>1.988</td>
</tr>
<tr>
<td>Bronchodilators (0 : No ; 1: Yes)</td>
<td>1.477</td>
<td>0.001</td>
<td>1.166</td>
<td>1.872</td>
</tr>
</tbody>
</table>

There was no interaction between treatment and each individual factor (age: p=0.080; FEV$_1$: p=0.05; number of previous AECB: p=0.247; acute bronchodilators: p=0.752).

Moxifloxacin had a beneficial effect versus comparator treatment on the occurrence of the composite event (OR=0.816) while other significant factors had a detrimental effect. The difference between antibiotic treatments in favour of moxifloxacin was primarily linked to benefits in the subgroup of patients aged ≥65 years (p=0.015) (Figure 1a&b). The global interaction term regarding the number of AECB was not significant but there was a statistically significant difference in favour of moxifloxacin in the subgroup of patients having had AECB equal or greater than 4 in the last year (p=0.047) (Figure 2a&b). Neither FEV$_1$ nor acute bronchodilator use played a role in the difference between antibiotic treatments.

**DISCUSSION**

The MOSAIC study has provided the opportunity to look in a systematic manner at the relative prognostic value of a number of factors related to medical history, clinical and functional status, and concomitant medications. Many factors identified in the univariate analysis were not retained in the multivariate analysis due to the large degree of co-variation between the individual factors.

The findings of this post hoc analysis of the MOSAIC study are similar to the published evidence that severity of airflow destruction, co-existing cardiopulmonary disease and the frequency of previous exacerbations were risk-factors for poorer short-term outcomes (23-30).
The number of previous AECB appeared to have a more powerful influence than age and duration of the disease, probably because repeated exacerbations are linked to disease progression. Whilst having cardiopulmonary disease as a co-morbid illness was a potent negative predictor of short-term outcome, BMI equal to or below 30kg/M² and diabetes did not play a role.

Current smoking habit has previously been associated with lower airway bacterial colonization but in this study it did not impact either clinical cure or clinical success (31, 32). This discrepancy could be due to the homogeneity of the study population and the lack of a reference group of non smokers. In fact, patients enrolled in the MOSAIC study were selected to increase the likelihood that bacterial infection was the cause of their exacerbation. They had to have the three cardinal symptoms of an Anthonisen type one exacerbation including increased breathlessness and sputum production, purulent sputum, and had a long history of chronic bronchitis due to cigarette smoking (1, 22). FEV₁ <50% predicted, the use of corticosteroids and the use of bronchodilators were all negative predictive factors of outcomes (the latter solely on clinical success) in univariate analyses. In the multivariate analysis though, the use of corticosteroids was no longer an independent predictive factor. Likely, this is explained by the high co-variation between those factors.

Regarding the long-term outcome, Ball et al had shown that a past history of frequent exacerbations made a future exacerbation more likely, a finding that is fully confirmed by the present study (24). Some patients are prone to frequent exacerbations, perhaps because their bronchial inflammation is poorly controlled and chronic bacterial infection may be the primary cause (13). Incomplete resolution of the index exacerbation, possibly due to persistent bacterial infection, would be expected to lead to a shorter interval until next exacerbation (5, 11). This hypothesis has led to the clinical endpoint of time until next exacerbation being used in antibiotic trials (22, 33). Moxifloxacin and gemifloxacin have given a longer time until next exacerbation compared to clarithromycin, a macrolide antibiotic, and older beta-lactam antibiotics. However, this has not been the outcome in all such comparator studies and the
severity of the exacerbation at enrolment, and the patients underlying disease may account for these differences. For example, in the study conducted by Lode et al (34) which did not demonstrate a difference in time until next exacerbation between levofloxacin and clarithromycin, a third of patients were non-smokers (cf zero in MOSAIC), a quarter had FEV\textsubscript{1} <50\% (cf 42\% in MOSAIC) and a quarter had Anthonisen type 2 exacerbations whereas all MOSAIC patients had type 1 exacerbations.

Similarly, FEV\textsubscript{1} <50\% predicted and acute use of bronchodilators appeared to be independent negative predictors of long-term outcome, while the use of corticosteroids had no predictive value there. Clinical interpretation of the findings of this post hoc analysis must be interpreted with caution given the exploratory nature of this analysis and the fact that corticosteroids and bronchodilators were not randomized in the trial. In the context of the MOSAIC study, the use of bronchodilators and/or corticosteroids, together with impaired FEV\textsubscript{1}, identified a patient subgroup at higher risk of failure, and further research will be needed to find out which of these three parameters has the best prognostic value in clinical practice. The data also suggest that use of bronchodilators, most likely to treat wheezing, might be a direct or indirect marker of disease severity which influences the short and long-term outcomes of antibiotic treatment, a hypothesis that could only be further tested in a randomized factorial design.

Another study design issue will require consideration in the future. The features of the exacerbation leading to antibiotic randomisation are defined by the Anthonisen type 1 criteria to capture a group of patients judged most likely to benefit from antibiotics (1). In the MOSAIC trial this was not true of the definition of treatment failure, nor of the next exacerbation, which were dependent on the doctors judgement of the need for further antibiotic treatment. This clinical decision might have been made because of features, such as level of breathlessness, that are dependent on other pathologies as well as bacterial infection. The early separation of the plots shown in Figures 1a and 2a suggest that the main long-term differences between the two
study groups were primarily accrued in the first six weeks, perhaps due to persistence of bacterial infection. This may be the time period for careful study of patients to try to define the reasons for clinical failure and the type of exacerbation that occurs with early recurrence following antibiotic treatment.

This analysis also sheds new light on the previously published clinical results of the MOSAIC study in that the overall beneficial effect of moxifloxacin on clinical resolution was confirmed when prognostic factors are taken into account. When using the less stringent clinical outcome criterion of clinical success (i.e. resolution and improvement combined), the primary unadjusted analysis of the trial had shown a not significant result (22). Interestingly, the subsequent statistical adjustment on prognostic factors unveiled a statistically significant difference between the two antibiotic treatment groups in favor of moxifloxacin. Likewise, in the primary analysis moxifloxacin was found to have a beneficial effect on the occurrence of the composite event in the first 5 months follow-up, a difference that was no longer significant at study completion (22). The present post-hoc analysis indicates that the beneficial effect of moxifloxacin was in fact sustained over the entire follow-up period when relevant prognostic factors were taken into account. That benefit was primarily accrued in two subsets of the study population: patients 65 years and those having experienced 4 or more exacerbations in the last year. This information could be used in the design of future prospective studies using time to next exacerbation as the primary endpoint.

Overall, this study showed that the number of past AECB and the baseline FEV₁ level were potent prognostic factors of the short and long-term treatment outcomes of AECB. Comorbid cardio-pulmonary diseases appeared to negatively affect the short-term outcome although no further explanation for this fact can be devised from the present analysis. The acute use of bronchodilators flagged a population at higher risk of failure in the longer term. Despite the choice of an homogeneous population of chronic bronchitis patients from the MOSAIC study
and the stratification of the randomisation on corticosteroids, between-group differences could still be confounded by underlying factors related to the medical history, the severity of the disease, and to the use of concomitant medications. It suggests that future clinical trials of antibiotic therapies in AECB systematically take these factors into account either a priori (at randomisation) or a posteriori (statistical analysis) in order to increase the sensitivity of studies to detect differences between antibiotic regimens.
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Figure

1a: Life-table analysis of time to the first composite event in patients with age ≥ 65 years (ITT population)

Figure 1b: Life-table analysis of time to the first composite event in patients with age < 65 years (ITT population)

Figure 2a: Life-table analysis of time to the first composite event in patients with number of previous AECBs ≥ 4 (ITT population)

Figure 2b: Life-table analysis of time to the first composite event in patients with 2-3 previous AECBs (ITT population)
Figure 1a: Life table analysis of time to the first composite event in patients with age ≥ 65 years (N=344)
Figure 1a: Life table analysis of time to the first composite event in patients with age ≥ 65 years (N=344)
Figure 1b: Life table analysis of time to the first composite event in patients with age < 65 years (N=380)
Figure 2a: Life-table analysis of time to the first composite event in patients with number of previous AECBs ≥ 4 (N=203)
Figure 2b: Life-table analysis of time to the first composite event in patients with 2-3 previous AECBs (N=522)
Figure 2a: Life-table analysis of time to the first composite event in patients with number of previous AECBs ≥ 4 (N=203)
Figure 2b: Life-table analysis of time to the first composite event in patients with 2-3 previous AECBs (N=522)

- **Patients not experiencing composite event (%)**
  - Time since randomisation (months)
  - Moxifloxacin
  - Comparator
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