METHODOLOGICAL ISSUES IN THERAPEUTIC TRIALS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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This research was funded by grants from the Canadian Institutes of Health Research (CIHR) and Fonds de la recherche en santé du Québec (FRSQ). The author is the recipient of a Distinguished Investigator award from the CIHR. The OPTIMAL trial database used for illustration was funded by grants from CIHR and the Ontario Thoracic Society.

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ABSTRACT (200 words)

The recent TORCH randomized trial replicated the findings of previous trials in chronic obstructive pulmonary disease (COPD) on the effectiveness of inhaled corticosteroids (ICS) in reducing exacerbation rates, but not so for mortality. We review methodological issues in these trials, such as patients already receiving ICS before randomization and the absence of follow-up after study drug discontinuation, using data from two trials. First, among previous ICS users in the OPTIMAL trial, the hazard ratio of the first exacerbation with inhaled corticosteroids relative to bronchodilators was 0.71 (95%CI:0.53-0.96;P=0.027), while among those not using ICS prior to randomization, it was 1.11 (95%CI:0.69-1.79;P=0.68). Second, the rate ratio of exacerbations with inhaled corticosteroids was 0.78 (95%CI: 0.61-0.99) prior to drug discontinuation and 1.23 (95%CI:0.78-1.95) thereafter. Finally, a 2x2 factorial analysis of the TORCH data found a rate ratio of mortality for the salmeterol component to be 0.83 (95%CI:0.74-0.95) while for the fluticasone component it was 1.00 (95%CI:0.89-1.13). We conclude that after proper consideration of various methodological shortcomings in the design and analysis of randomised trials, the effectiveness of inhaled corticosteroids in treating COPD remains doubtful, while the benefit observed with combination therapy may rather be due exclusively to the beneficial effects of the long-acting bronchodilator alone.

Key words: Data analysis; Biases; Drug effectiveness; Databases; Methods; Chronic Obstructive Pulmonary disease; inhaled corticosteroids;
INTRODUCTION

The recently published TORCH trial has provided the field of chronic obstructive pulmonary disease (COPD) therapeutics with a landmark study that undoubtedly advanced our knowledge about the potential benefits of inhaled corticosteroids and long-acting bronchodilators in the treatment of this disease.[1] The TORCH study also illustrates several methodological issues pertinent to the proper conduct of randomized trials in COPD. While this major study answers important questions as to the role of inhaled corticosteroids in potentially preventing mortality in COPD, major questions related to the role of inhaled corticosteroids (ICS) in preventing exacerbations of COPD remain unanswered.

Major randomized controlled trials that have evaluated the effectiveness of inhaled corticosteroids in the treatment of COPD over the last decade have reported results that are often contradictory and that seem paradoxical.[2, 3] Generally, these studies have found that inhaled corticosteroids had either no effect, or only minor beneficial effects, on decline in lung function as measured by FEV1, the primary outcome measure. On the other hand, most of these trials have observed significant reductions in COPD exacerbation rates associated with ICS use; a meta-analysis of these trials suggested a clinically significant reduction in exacerbations of approximately 30%.[4] Much of this apparent benefit reported in the meta-analysis, was the result of an incorrect statistical approach to the analysis of these exacerbations.[5] Indeed, many of the previously performed trials used statistically flawed, unweighted analyses of exacerbations, and therefore failed to incorporate correction of overdispersion into their
analyses. Two subsequent trials that used the proper statistical approach, demonstrated a modest reduction, albeit non significant, in the rate of COPD exacerbations.[6, 7] In addition to a reduction in exacerbations, a pooled analysis of data from seven randomised trials involving over 5,000 patients reported a significant 27% reduction in all-cause mortality associated with ICS use.[8]

Thus, paradoxically, inhaled corticosteroids would do little to improve lung function, itself strongly related to mortality [9] and probably to frequency of exacerbations [10], but could prevent significant numbers of COPD exacerbations and deaths from all causes. While various physiological explanations such as effects on systemic inflammation [11], have been put forward to explain a benefit on exacerbations and mortality in the face of no benefit on lung function, possible methodological explanations for these discrepant results have received little attention.

In this paper, we review several key aspects of the design and statistical analysis of COPD intervention trials including the TORCH trial, and illustrate these issues using data from the OPTIMAL randomised trial.

DATA FOR ILLUSTRATION

The Canadian OPTIMAL study was a three-arm randomized trial of 449 patients with moderate or severe COPD all given a base therapy of tiotropium and allocated randomly to receive, in addition, placebo (N=156), salmeterol (N=148), or fluticasone/salmeterol (N=145).[12] The primary outcome was a COPD exacerbation requiring treatment with oral or intravenous steroids and/or antibiotics within the year
after randomization. Outcomes were recorded over the entire one-year follow-up period, regardless of whether patients had discontinued the study medications. A patient was considered to have experienced a new COPD exacerbation if they had not taken oral steroids and antibiotics for at least 14 days following their previous exacerbation.

Since the issue at hand involves the potential benefit of inhaled corticosteroids, we combined the 304 patients randomized to tiotropium with or without salmeterol (we call this the bronchodilator group) and compared them with those randomized to the two bronchodilators plus fluticasone (the inhaled corticosteroid group). This regrouping is also justified by the similar results obtained whether tiotropium was combined with placebo or with salmeterol. We used information on the dates of exacerbations, the use of inhaled corticosteroids prior to randomization and the date of discontinuation of study medications during follow-up to illustrate the methodological issues relevant to COPD trials.

METHODOLOGICAL ISSUES

Most randomized trials to assess the effectiveness of inhaled corticosteroids in COPD conducted to date have had several unique features and limitations: 1) many patients were already receiving inhaled corticosteroids before randomization; 2) analyses did not look specifically beyond the first exacerbation; 3) the trials stopped following the patients who discontinued the study drugs before the end of the observation period. Furthermore, several trials, including the TORCH study did not fully exploit the data available from their unique 2x2 factorial design. We now describe these
issues and show how they can impact the results and interpretation of trials of therapy in COPD.

**Previous therapy**

The various trials of inhaled corticosteroids in COPD have been conducted, at least in part, among patients already using these medications before randomization. This is an exceptional situation for randomized trials. The proportion of patients who were previous users of these drugs in the placebo group varied from 26% in the Szafranski study [6] to 51% in the TORCH trial and as high as 77% in the OPTIMAL trial. In all these trials, the patients were of course required to stop their inhaled corticosteroids at the time of randomisation. This unusual situation creates a unique challenge in interpretation. Indeed, among the patients who did not previously use inhaled corticosteroids, the randomisation will lead to the desired comparison of patients initiating treatment with ICS with similar patients who do not. On the other hand, among the patients who were previous regular users of inhaled corticosteroids, the randomisation will in fact provide a comparison of patients who continue to use ICS (patients allocated to ICS treatment) and patients who discontinue ICS (patients allocated to placebo). Figure 1 depicts this phenomenon. Thus, among previous users of inhaled corticosteroids, the randomized trial will in fact evaluate the effect of stopping the use of ICS; albeit perhaps a different ICS and at a different dose, rather than the effect of introducing ICS as treatment.
A potentially analogous situation occurs in trials of tiotropium, when patients are obliged to stop their short-acting anti-cholinergic bronchodilator, ipratropium bromide, and in some studies their long-acting beta-agonist as well, at the time of randomization so that those allocated to placebo are in fact being withdrawn from therapy with anti-cholinergic bronchodilators and possibly other bronchodilators.[13-17]

Using the illustrative data from the OPTIMAL trial, we stratified the patients according to their previous use of inhaled corticosteroids and studied the time from randomisation to the first COPD exacerbation. Figure 2a shows the Kaplan-Meir curves for the time to the first exacerbation among the patients who were previous users of inhaled corticosteroids (N=335) for the randomised bronchodilator and inhaled corticosteroids groups. Figure 2b displays the corresponding curves among the patients who were naïve to inhaled corticosteroids (N=114) at the time of randomisation. It is evident that the effects are different. Table 1 provides the corresponding hazard ratios estimated from the proportional hazards model. The hazard ratio of the time to first exacerbation for the inhaled corticosteroid group relative to the bronchodilator group is 0.79 (95% CI: 0.62-1.02; P=0.07) for the analysis including all subjects. However, among the patients who had previously used ICS, the hazard ratio is 0.71 (95% CI: 0.53-0.96; P=0.027), while for those who had not used ICS, it was 1.11 (95% CI: 0.69-1.79; P=0.68). This latter estimate, however, is based on only 30% of the subjects and thus has lower power. While its best estimated value is 1.11, it is also compatible with a value of 0.69, the lower bound of the 95% confidence interval.
We reviewed this relationship in all RCTs of ICS conducted in patients with COPD that provided both the rate ratio of exacerbations and information on the prior use of ICS (Table 2). Figure 3 shows the plot of the rate ratio of exacerbation across the studies against the rate of ICS use prior to randomization. The corresponding generalized linear model analysis of the logarithm of the rate ratio on the rate of ICS use prior to randomization, weighted by the inverse of its variance, resulted in a reduction of 8% in the rate ratio (RR 0.92; 95% CI: 0.89-0.96; P<0.001) for every 25% increase in the rate of prior ICS use.

**Beyond the first exacerbation**

While all randomized trials have studied the rate of exacerbation while subjects were being followed and some trials have analyzed the time to the first COPD exacerbation, none has specifically examined the pattern of COPD exacerbations subsequent to the first one. In particular, we might ask how much of the effect of the treatment on the rate of exacerbation measured over the entire follow-up is due to its effect on the first COPD exacerbation. To investigate this question, we considered the subgroup of patients with at least one COPD exacerbation in the OPTIMAL trial. This included 87 patients in the inhaled corticosteroid group and 186 in the bronchodilators group. We analysed the time from the end of their first COPD exacerbation to the onset of the second one, censoring the patients who did not have a second one at the last follow-up. Figure 4 shows the Kaplan-Meir curves for the time from the first to the second COPD exacerbation according to randomisation to the bronchodilator or inhaled
corticosteroids groups. The corresponding hazard ratio of the second exacerbation for the inhaled corticosteroid group relative to the bronchodilator group is 1.00 (95% CI: 0.73-1.40; P=0.96), as shown in Table 1. Since this analysis is by the intention-to-treat approach and performed in the subset of the population with an exacerbation during follow-up, the interpretation is complex. However, fewer than 10% of the subjects in this analysis had discontinued their allocated treatment during follow-up but prior to their first exacerbation (starting point for this analysis). Nevertheless, this analysis suggests that the effect of ICS on the rate of exacerbation over the study period may be dominated by its effect on first exacerbation. This contrasts with trials of ICS in combination with bronchodilators in asthma where the relative benefits increase with each exacerbation.[18]

**Extent of follow-up**

Up until the TORCH and OPTIMAL studies, randomized trials of COPD therapy stopped patient follow-up at the time they discontinued the study drug. Thus, any outcome information after the patients were withdrawn, but before the planned end of study follow-up, was not collected. As such, the fundamental intent-to-treat analysis for such trials was not possible since the data were truncated at the time of drug discontinuation. While the extent of this problem may be trivial in other diseases, COPD trials characteristically demonstrate very high discontinuation rates and such drop outs often occur very early in the trial. Not following patients up until the end and conducting the data analysis only until discontinuation of study drugs will produce biased results if
the reason for discontinuation is associated with the outcome and differs between treatments. The importance of this principle was clearly demonstrated by the Coronary Drug Project Research Group, which showed that patients who were not compliant with placebo, just like those who were not compliant with clofibrate, had significantly higher mortality than those “properly treated” patients who took their placebo regularly.[19] Thus, considering only the “compliant” follow-up time prior to discontinuation can lead to bias.

Table 2 also shows that the withdrawal rates were variably different between treatment groups in the randomised controlled trials comparing an inhaled corticosteroid to placebo in patients with COPD. The corresponding generalized linear model analysis, adjusted for prior ICS use, resulted in an increase of 3% in the rate ratio of exacerbation (RR 1.03; 95% CI: 1.01-1.06; P=0.011) for every 10% increase in the ratio of withdrawal rates between the ICS and placebo groups. This suggests that the studies with the greatest disparity in withdrawal rates found the largest reduction in the rate of exacerbation with ICS compared with placebo.

To avoid such bias, the TORCH trial correctly followed all patients up to the end of the three-year trial period to ascertain mortality, its primary outcome, even after discontinuation of the study medications. This was not done, however, for the secondary outcomes including exacerbations, lung function and health status. This is of concern since 44% of patients in the placebo group discontinued treatment, mostly during the first few months, as compared with 34% in the combination therapy group. Thus, for the TORCH trial, the intent-to-treat results for mortality are certainly valid,
however the results describing the secondary outcomes and in particular exacerbations, may be biased.

To investigate the potential effect of this bias, we used data from the OPTIMAL study that did aim to follow up patients for the entire 1-year study period. Despite the attempt to follow up each patient, 65 of the 449 patients could not be followed up beyond drug discontinuation because of withdrawal of patient consent, while 110 of the patients who prematurely discontinued study drugs were followed up for the duration of the 12-month trial period. This dataset provides sufficient numbers of fully followed patients to evaluate this potential bias. Table 2 shows the rates of COPD exacerbation when ascertained over the entire follow-up period and when restricted to the period until discontinuation of study drugs. The rate ratio of exacerbation with inhaled corticosteroids using the entire follow-up time is 0.83 (95% CI: 0.66-1.04), while it is 0.78 (95% CI: 0.61-0.99) prior to drug discontinuation and 1.23 (95% CI: 0.78-1.95) thereafter.

With respect to mortality, there exists a major discrepancy between a pooled analysis of seven major randomized trials, involving 5,086 patients, that found a significant 27% reduction in mortality with inhaled corticosteroids (hazard ratio 0.73; 95% CI: 0.55-0.96; P=0.039), and the TORCH trial that found no reduction whatsoever with fluticasone.[1, 8] Trials that comprised the pooled analysis truncated patient follow-up when they discontinued the study drug. The pooled analysis in fact found no difference in mortality during the first 9 months of follow-up, the time period where drop-outs were still rare and thus where most randomized patients were included in the
mortality analysis. The apparent benefit of ICS was in fact only visible after 9 months. While the mortality rate in the ICS group is stable over time, the benefit is the result of two clusters of deaths in the placebo group occurring at precisely the 9th and 24th months of follow-up.\[20\] On the other hand, the TORCH trial that followed all patients up for 3 years found a hazard ratio of mortality for fluticasone relative to placebo of 1.06 (95% CI: 0.89-1.27; P=0.53).\[1\] This disagreement between the two large mortality studies is thus likely a direct result of the follow-up process.

**Factorial analysis of TORCH data**

While the TORCH study aimed to compare the combination of fluticasone and salmeterol with placebo, the study also included a fluticasone only and a salmeterol only arm.\[1\] This study was thus structured as a 2x2 factorial design of fluticasone (yes/no) and salmeterol (yes/no). This same factorial design was also used in other trials involving an inhaled corticosteroid and a long-acting beta-agonist.\[6, 7, 21\] However, all these trials including TORCH were not analyzed as factorial trials, thus squandering much needed power and denying the reader important information about the independent contribution of each component of the combination.

As mortality was the only outcome ascertained in a complete manner for an intent-to-treat analysis, we used the mortality data presented in the TORCH paper to perform the analysis corresponding to a 2x2 factorial design as has been previously reported by La Vecchia and Fabbri [22]. We used a generalized linear model with a binomial distribution to estimate the 3-year mortality rate ratio associated with
fluticasone and salmeterol. We furthermore used an interaction term to assess whether there is synergy between the two drugs. We found that the interaction term was not significant (P=0.32) suggesting that the combination of fluticasone and salmeterol is not particularly more effective than the two components added independently. Table 3 presents the rates and the independent effects of fluticasone and salmeterol on mortality, namely adjusted for each other. While the salmeterol component is associated with a significant 17% reduction in mortality (rate ratio 0.83; 95% CI: 0.74-0.95; P=0.0043), the fluticasone component provides no reduction whatsoever (rate ratio 1.00; 95% CI: 0.89-1.13; P=0.9918).

Unfortunately, this analysis is invalid for the other outcomes such as exacerbations and health status since these were not measured throughout the entire follow-up. They are thus also subject to the bias described above resulting from truncating patient follow-up at the discontinuation of assigned drug therapy.

DISCUSSION

Randomized controlled trials conducted to assess the effectiveness of inhaled corticosteroids over the past decade have reported results that appear paradoxical. While these drugs were found to have no or only minor effects on lung function in earlier studies, they were associated with significant reductions in COPD exacerbation rates, as well as significant reductions in mortality in pooled studies. We showed that unique methodological aspects of the study design and statistical analysis of these studies at least partly explain this apparent paradox. After accounting for several characteristics of
the analytic techniques used in these studies, as illustrated using the OPTIMAL trial data, we found that an apparent benefit of inhaled corticosteroids disappears.

The single most important methodological concern is the rather unique situation in COPD of randomising some patients who were already being treated with inhaled corticosteroids before randomisation, to treatment with inhaled corticosteroids after randomisation. This unusual situation creates in actuality two types of comparison. Among the patients who did not use inhaled corticosteroids previously (ICS-naïve), the randomisation will lead to a comparison of patients initiating treatment with ICS with similar patients who do not. Among previous users of inhaled corticosteroids, however, the randomisation will lead to a comparison of patients who continue ICS use with patients who stop their use of ICS. Thus, combining previous users with non-users in these trials leads to a mixture of the true effect of inhaled corticosteroids (ICS-naïve patients) with the effect of suddenly interrupting inhaled corticosteroids (previous users). Our illustration using data from the OPTIMAL trial showed that among the ICS-naïve patients at randomisation, there was no benefit whatsoever with inhaled corticosteroids on the rate of exacerbation or the time to the first exacerbation. Thus, the apparent effect seen among all patients combined was exclusively due to the effects in the subgroup that had previously used ICS. In actuality, these trials therefore measure the effects of stopping ICS rather than introducing ICS. There are studies which have directly examined the effect of stopping ICS and have found either a decrease in lung function or a similar increase in exacerbations.[23, 24] Such a deleterious effect of stopping ICS does not necessarily translate to a beneficial effect of initiating such
therapy. This design aspect is not unique to ICS, as it was also observed in the trials of tiotropium.

Another crucial methodological issue is the design of trials in which follow-up is ended at the time patients discontinue using the study drug. As a result, outcome data after patient withdrawal are missing so that an authentic intent-to-treat analysis becomes impossible. The analysis based on data censored at drug discontinuation, equivalent to restricting the analysis to the compliant patients, introduces intricate biases that are difficult to disentangle. The TORCH trial did correctly follow all patients after discontinuation of study medications to ascertain mortality, but did not do this for exacerbations, lung function and health status outcomes. Thus, with almost half of patients discontinuing treatment, the results are valid for mortality, but can be biased for exacerbations and for other outcomes. The OPTIMAL trial, that did measure outcomes to the end of follow-up, found different results for the exacerbation rates when the data were analysed over the entire follow-up compared with follow-up censored at drug discontinuation.[12] Future trials will necessarily have to follow patients to the end of follow-up and continue to obtain measures of important outcomes after drug discontinuation. To minimise such bias, studies may envisage a shorter more manageable follow-up (one or two years) that will decrease the number of patients actually lost to follow-up.

Other methodological aspects of these studies can also have a bearing on the results. Many studies did not look specifically at the time to the first exacerbation and the subsequent pattern, particularly the time from the first to the second exacerbation.
The use of the negative binomial model to fit the exacerbation rate in the TORCH study needs to be evaluated and compared with the straightforward Poisson model that accounts for the between-patient variability in the exacerbation rate with an overdispersion parameter.[5] Important differences between these approaches were found with the OPTIMAL data.[25]

Finally, the studies designed as 2x2 factorial trials to assess the effects of an inhaled corticosteroid and a long-acting beta-agonist, such as the TORCH study, did not exploit fully the data by using the corresponding 2x2 factorial data analysis. When this 2x2 analysis was performed for the TORCH study, there was no evidence of a synergistic effect from the combination of salmeterol and fluticasone; the observed benefit was entirely due to the effect of salmeterol, with no effect whatsoever attributable to the inhaled corticosteroid component.

The randomised controlled trial is and will remain the fundamental tool to evaluate the benefit of COPD treatments. Its proper conduct, however, including the most rigorous study design and data analysis, is essential to the production of valid results. The TORCH and OPTIMAL trials have provided an important evolution in this direction with designs that allowed a proper intent-to-treat analysis of the primary outcomes. These analyses showed no clear substantiation of the added benefit of inhaled corticosteroids in COPD. The science of COPD research is, however, still faced with major challenges involving a complex and serious disease requiring multiple treatments, pharmacologic and non-pharmacologic, and with highly variable outcomes. The corresponding methodological complexities will have to be tackled to prevent the
dissemination of studies that will bring false hope to the makers, prescribers and users of medications such as inhaled corticosteroids. With COPD one of the major causes of morbidity and mortality worldwide, the responsibility for the utmost scientific rigor in the design and analysis of studies in this domain befits us all.
Reference List


### Table 1
Analyses of the effect of inhaled corticosteroids compared with bronchodilators on the time to first and second exacerbation using the OPTIMAL study data

<table>
<thead>
<tr>
<th>Median time to exacerbation (days)</th>
<th>Inhaled corticosteroids</th>
<th>Bronchodilators</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time to first exacerbation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All subjects (N=449)</td>
<td>224</td>
<td>136</td>
<td>0.79 (0.62-1.02)</td>
</tr>
<tr>
<td>Prior ICS* users (N=335)</td>
<td>209</td>
<td>116</td>
<td>0.71 (0.53-0.96)</td>
</tr>
<tr>
<td>No Prior ICS use (N=114)</td>
<td>248</td>
<td>250</td>
<td>1.11 (0.69-1.79)</td>
</tr>
<tr>
<td><strong>Time from first to second exacerbation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All subjects (N=273)</td>
<td>111</td>
<td>129</td>
<td>1.00 (0.73-1.40)</td>
</tr>
</tbody>
</table>
Table 2

Randomised controlled trials comparing an inhaled corticosteroid (alone) to placebo that include data on the rate ratio of exacerbation and previous use of inhaled corticosteroids prior to randomisation

<table>
<thead>
<tr>
<th>Inhaled corticosteroids</th>
<th>Placebo</th>
<th></th>
<th></th>
<th>Prior ICS use (%)</th>
<th>Rate ratio of exacerbation</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Withdrawal (%)</td>
<td>N</td>
<td>Withdrawal (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td>-----</td>
<td>----------------</td>
<td>-----</td>
<td>----------------</td>
<td>---------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Vestbo[26]</td>
<td>145</td>
<td>25</td>
<td>145</td>
<td>35</td>
<td>0</td>
<td>0.96</td>
</tr>
<tr>
<td>ISOLDE[27]</td>
<td>372</td>
<td>43</td>
<td>370</td>
<td>53</td>
<td>57</td>
<td>0.75</td>
</tr>
<tr>
<td>Szafranski[6]</td>
<td>198</td>
<td>31</td>
<td>205</td>
<td>44</td>
<td>26</td>
<td>0.85</td>
</tr>
<tr>
<td>TRISTAN[21]</td>
<td>374</td>
<td>29</td>
<td>361</td>
<td>39</td>
<td>52</td>
<td>0.81</td>
</tr>
<tr>
<td>Calverley[7]</td>
<td>257</td>
<td>40</td>
<td>256</td>
<td>41</td>
<td>46</td>
<td>0.89</td>
</tr>
<tr>
<td>TORCH[1]</td>
<td>1534</td>
<td>38</td>
<td>1524</td>
<td>44</td>
<td>51</td>
<td>0.82</td>
</tr>
</tbody>
</table>

* Not reported in the paper; computed from a comparison of two Poisson counts
Table 3
Analyses of the effect of inhaled corticosteroid use compared with bronchodilators on the rate of exacerbation over different follow-up periods using the OPTIMAL study data

<table>
<thead>
<tr>
<th>Follow-up period</th>
<th>Rate of exacerbation (per year)</th>
<th>Inhaled corticosteroids</th>
<th>Bronchodilators</th>
<th>Rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire observation period (N=449)</td>
<td></td>
<td>1.39</td>
<td>1.67</td>
<td>0.83 (0.66-1.04)</td>
</tr>
<tr>
<td>Until discontinuation only (N=449)</td>
<td></td>
<td>1.30</td>
<td>1.69</td>
<td>0.78 (0.61-0.99)</td>
</tr>
<tr>
<td>After discontinuation (N=137)</td>
<td></td>
<td>2.02</td>
<td>1.64</td>
<td>1.23 (0.78-1.95)</td>
</tr>
</tbody>
</table>
Table 4

Factorial analysis of TORCH data of the independent effects of fluticasone and salmeterol on the 3-year incidence of all-cause mortality

<table>
<thead>
<tr>
<th>Medication allocated</th>
<th>Crude RR</th>
<th>Adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone</td>
<td>1.00</td>
<td>1.00 (0.89-1.13)</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>0.83</td>
<td>0.83 (0.74-0.95)</td>
</tr>
<tr>
<td>Yes</td>
<td>(Deaths/N)</td>
<td>(Deaths/N)</td>
</tr>
<tr>
<td>No</td>
<td>436 / 3045</td>
<td>477 / 3058</td>
</tr>
</tbody>
</table>
LEGEND FOR FIGURES

1. Depiction of a typical randomized trial of COPD patients already using the study drug, namely inhaled corticosteroids, prior to randomisation, who are then randomised to either inhaled corticosteroids or placebo.

2. Kaplan-Meir curves for the time to the first exacerbation comparing the patients randomised to either inhaled corticosteroids or bronchodilators among: a) the 335 patients who were previous users of inhaled corticosteroids at the time of randomisation; b) the 114 patients who were naïve to inhaled corticosteroids at the time of randomisation (data from the OPTIMAL trial).

3. Plot of rate ratio of exacerbations by the proportion of users of inhaled corticosteroids prior to randomisation in all six randomised controlled trials comparing an inhaled corticosteroid (alone) to placebo that include these necessary data. This line corresponds to the fitted generalised linear model for these rate ratios, weighted by the inverse of the variance.

4. Kaplan-Meir curves for the time from the first to the second exacerbation comparing the patients randomised to either inhaled corticosteroids or bronchodilators, among the 273 patients who had an exacerbation (data from the OPTIMAL trial).
Figure 1
PRIOR USERS OF ICS

Cumulative first exacerbation-free proportion

0 90 180 270 360
Time of follow-up (days)

Inhaled corticosteroids
Bronchodilators

NON PRIOR USERS OF ICS

Cumulative first exacerbation-free proportion

0 90 180 270 360
Time of follow-up (days)

Inhaled corticosteroids
Bronchodilators

Figure 2a

Figure 2b
Figure 3
Figure 4

[Graph showing the cumulative second exacerbation-free proportion against time of follow-up (days).]

- Inhaled corticosteroids
- Bronchodilators