

# RAPID APPRAISAL

**Name of Trial:** Salmeterol and Fluticasone Propionate and survival in chronic obstructive pulmonary disease (TORCH trial).

**Reference:** Calverley PMA, Anderson JA, Celli B et al. N Engl J Med: 2007;356:775-89.

**Question:** Does treatment with a combination of salmeterol and fluticasone reduce mortality in patients with chronic obstructive pulmonary disease compared with placebo, salmeterol or fluticasone alone?

**Summary:** Combination treatment with salmeterol and fluticasone failed to demonstrate a significant difference in the mortality rate of patients with moderate to severe COPD over three years. When compared with placebo, the hazard ratio for death due to any cause was 0.825 (95%CI 0.681 to 1.002) which was not statistically significant ( $p = 0.052$ ). Although significant differences in other measures were demonstrated, the study was not powered to detect changes in the secondary endpoints.

## ***Did the study ask a clearly focussed question?***

**Yes** – This study was designed to compare the effect of combination treatment (salmeterol and fluticasone), placebo, and each of the components alone on mortality over three years in patients with chronic obstructive pulmonary disease (COPD).<sup>1</sup> Prior to the study, all treatment with inhaled corticosteroids (ICS) or long-acting beta<sub>2</sub> agonists (LABAs) was stopped. After a two week run-in period, patients were randomly assigned to three years of treatment with combination therapy (salmeterol 50 micrograms and fluticasone 500 micrograms,  $n = 1,533$ ), salmeterol 50 micrograms ( $n = 1,521$ ), fluticasone 500 micrograms ( $n = 1,534$ ) or placebo ( $n = 1,524$ ). Each treatment was inhaled twice daily (morning and evening) as a dry powder via an Accuhaler® device. The primary outcome measure was the time to death from any cause by three years. Secondary outcome measures were frequency of exacerbations and health status (measured using the St George's Respiratory Questionnaire).

## ***Was the study design appropriate?***

**Yes** – The TORCH trial was a prospective, double-blind, placebo-controlled, randomised, parallel-group study. Eligible patients were current or former smokers with at least a 10-year pack history (e.g. 10 years of smoking one pack per day), aged between 40 and 80 years, a clinical diagnosis of COPD, FEV<sub>1</sub> of <60% predicted, a post-bronchodilator increase in FEV<sub>1</sub> < 10%, and a FEV<sub>1</sub>/FVC ratio of  $\leq 0.7$ . Patients with concomitant conditions likely to interfere with the study or cause death within three years and those requiring long term ( $\geq 12$  hours per day) oxygen therapy were excluded from the trial.

Patients who experienced exacerbations that required systemic corticosteroids and/or hospitalisation during the run-in period were not eligible for randomisation.<sup>2</sup> Patients were allowed to continue any concomitant medication for COPD except ICS, LABAs and long-term oral steroids. All patients were offered salbutamol as relief medication.<sup>2</sup> An independent safety and efficacy data monitoring committee performed safety reviews every six months and two interim efficacy analyses were performed, the first after 358 deaths and the second after a total of 680 deaths. The study was supported by GlaxoSmithKline and all treatments used were products manufactured by this company. They were also involved in the study design and statistical analysis of results.

## ***Were participants appropriately allocated to intervention and control groups?***

**Yes** – Patients were randomised to one of four treatment arms using a 1:1:1:1 ratio. Randomisation was determined using a computer allocation system and was stratified by smoking status.<sup>2</sup>

## ***Were participants, staff and study personnel 'blind' to participants study group?***

**Yes** – Both patient and investigators were blind to treatment allocation. The dosing schedule and inhaler devices were identical in each treatment arm. An independent, blinded group reviewed and categorised the cause of death for each subject where this was recorded.<sup>2</sup>

## ***Were all of the participants who entered into the trial accounted for at its conclusion?***

**Yes** – In total, 8,554 patients were recruited and entered the run-in phase where any current ICS

and LABA treatment were discontinued. Almost 28% of these patients withdrew during the run-in period. Of these patients, 1,638 were withdrawn as they did not meet the inclusion criteria, the reasons for which were not specified but may have included exacerbations experienced during the run-in period. Of the 6,184 patients randomised to treatment 72 were excluded from the efficacy analysis as five centres failed to meet the standards for Good Clinical Practice and ethical practices. The study investigators reported that a *post-hoc* analysis in which these 72 patients were included did not materially change the outcome measures.<sup>3</sup> All patients randomised to treatment were included in the safety analysis.

### ***Were the participants in all groups followed up and data collected in the same way?***

**Yes** – All patients were followed up until three years after initiation of treatment, regardless of whether they continued to take the study medication. Patients were seen every 12 weeks to confirm vital status, record any unscheduled visits to a healthcare provider and note the occurrence of any adverse events. Post-bronchodilator spirometry was undertaken and health status assessed every 24 weeks.

### ***Was the study large enough?***

**Can't tell** – The design of the study required a minimum of 1,510 patients in each study group to detect a reduction in mortality of 4.3% in the combination therapy group as compared with the placebo group (hazard ratio for death 0.728) at a two-sided alpha level of 0.05 with 90% power. Power calculations were conducted assuming a 17% mortality rate in the placebo group based on data from the ISOLDE trial<sup>4</sup> however, mortality within the placebo group in this study was only 15.2%. The sample size was therefore increased two years after commencing study enrolment.<sup>3</sup> There were also a large number of drop outs from all arms of the study which will have diluted the statistical power of the study.<sup>3</sup>

### ***How are the results presented and what is the main result?***

The differences in time to death due to any cause (primary endpoint) were presented as hazard ratios (HRs) for the treatment group relative to the placebo group. These results were analysed using the log-rank test, with stratification according to smoking status. The probability of death at three years within the study was 15.2% in the placebo group compared with 12.6% in the combination group (13.5% and 16.0% in the salmeterol and fluticasone groups, respectively). The HR for combination therapy versus placebo therapy was 0.825 (95% CI 0.681 to 1.002,

$p = 0.052$ ). This result demonstrated there was no statistically significant difference in mortality rate between the two groups.

Sub-group analysis of the number of COPD-related deaths also failed to demonstrate any significant improvement with active therapy compared with placebo. There were no significant differences in the primary cause of death among the groups.

The frequency of exacerbations was analysed using a linear model. The annual rate of moderate to severe exacerbations and those requiring systemic corticosteroids were significantly reduced in each of the active treatment groups. Combination therapy also showed improvements in these exacerbation rates compared with the individual components (HR = 0.88 and 0.71 compared with salmeterol, HR = 0.91 and 0.87 compared with fluticasone, respectively). With respect to severe exacerbations requiring hospitalisation, both combination therapy and salmeterol alone reduced the annual rate significantly compared with placebo (HR 0.83 and 0.82,  $p = 0.03$  and 0.02, respectively).

Statistically significant changes in quality of life scores (St George's Respiratory Questionnaire) were observed with both treatment arms containing fluticasone; however neither reached the clinically significant threshold of four units.

### ***How precise are the results?***

This was a moderately sized phase III, multi-centred, randomised, controlled trial. Baseline characteristics were similar for each group. Within the placebo group 44% of patients ( $n = 673$ ) withdrew from the study prior to completion of three years treatment. Treatment with salmeterol, fluticasone or combination therapy demonstrated smaller drop-out rates; 37%, 38% and 34% respectively. All available data up to the time of discontinuation were included in the analysis; mortality data continued to be collected for subjects who withdrew early, up to three years after the start of treatment.

Due to the unexpectedly low mortality rate in the placebo group the  $p$  value for the primary comparison between the combination and placebo was adjusted upward to conserve an overall significance level of 0.050. The unadjusted HR for the primary endpoint was 0.82 (0.667 to 0.993,  $p = 0.04$ ) however the adjusted HR was reduced to 0.825 (0.681 to 1.002). The wide confidence intervals associated with the primary end point reached the line of no effect and indicate no statistically significant difference. As the primary endpoint did not reach statistical significance, changes in secondary outcomes which the study was not powered to detect, should be considered with caution.

### **How safe were the regimens?**

Within the three-year study period, 90% of patients reported experiencing an adverse event. Of these, 41% were classed as serious adverse events. Adverse events were responsible for the withdrawal of 1,318 patients (21%) from the study prior to completion. The most commonly reported event was exacerbation of COPD. The annual rate was 0.92 in the placebo group, 0.76 in the salmeterol group, 0.78 in the fluticasone group and 0.67 in the combination therapy group. No statistical analysis of the differences among these groups was reported. Other commonly reported adverse events included upper respiratory tract infection, nasopharyngitis, pneumonia, bronchitis, headache, back pain, sinusitis, cough and hypertension. There was a significant increase in the incidence of pneumonia in the fluticasone (18.3%) and combination therapy (19.6%) groups compared with placebo (12.3%,  $p < 0.001$ ). Monitoring for adverse events thought to be related to the use of high-dose inhaled corticosteroids revealed no significant differences in bone mineral density, fracture rate or incidence of cataracts with fluticasone-containing treatment arms.

### **Can the results be applied to the local population?**

The TORCH study comprised patients with a diagnosis of COPD and an FEV<sub>1</sub> of < 60% predicted and therefore would include patients with mild, moderate and severe COPD.<sup>5</sup> The results from this trial support the recommendation that combined ICS and LABAs are not appropriate for all patients with COPD. NICE

guidance published in February 2004 states that ICS (licensed in combination with LABAs) should be considered in patients with moderate to severe COPD (FEV<sub>1</sub> of  $\leq 50\%$  predicted) who have experienced two or more exacerbations requiring treatment with antibiotics or oral corticosteroids in the preceding 12 months. Of the patients involved in this trial, 48% were being treated with an ICS or combination therapy prior to inclusion, and 57% had experienced one or more exacerbations in the preceding 12 months. The study population did not match the group of patients for which NICE recommends a combination of ICS and LABA. In addition, patients in this trial were closely monitored which is likely to have improved their compliance with treatment, therefore the results may not be achievable under normal conditions.

### **Does treatment with a combination of salmeterol and fluticasone reduce mortality in patients with chronic obstructive pulmonary disease?**

**No** - This study showed no difference in the probability of death after three years of treatment with combination therapy (fluticasone plus salmeterol) compared with placebo (HR 0.825 95% CI 0.681 to 1.002,  $p = 0.052$ ). As this primary endpoint did not reach statistical significance, the secondary outcomes should be considered with caution. Treatment with ICS and a long-acting bronchodilator should be reserved for patients with an FEV<sub>1</sub>  $\leq 50\%$ , two or more exacerbations in the preceding 12 months and symptoms that are not controlled with short-acting bronchodilators.

## **REFERENCES**

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