



No increase in serious asthma events occurs with fluticasone plus salmeterol, study shows

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Patients with asthma who were treated with a fixed dose combination of the long acting beta-agonist (LABA) salmeterol plus the inhaled glucocorticoid fluticasone had no higher risk of asthma related death or hospital admission than those on fluticasone alone,¹ shows a randomised study that provides some reassurance after previous safety concerns.

But an accompanying editorial warned that the findings may not apply to patients with the most severe and unstable disease—the patients that guidelines say should be treated with LABAs plus inhaled glucocorticoid as first line therapy—because they were excluded from the study.²

Two previous large trials showed more asthma related deaths with salmeterol than with the short acting agent salbutamol, and in 2008 the US Food and Drug Administration asked LABA manufacturers to analyse all of their data to assess rates of serious asthma related events. Inhaled steroids were not part of routine asthma care at the time, but, as their use increased, the FDA asked LABA manufacturers to also assess the safety of treatment with a combination of LABAs plus an inhaled glucocorticoid.

The new study, funded by GlaxoSmithKline, randomly allocated 11 679 adolescent and adult patients (aged 12 and over) with persistent asthma to either fluticasone with salmeterol delivered in a single inhaler or to fluticasone alone for 26 weeks. All of the patients had had a severe asthma exacerbation in the year before randomisation but not in the previous month. Patients were excluded if they had a history of life threatening or unstable asthma.

Results from both treatments showed similar rates of asthma related deaths, endotracheal intubation, and hospitalisation. A

total of 36 serious asthma related events occurred in 34 patients given fluticasone plus salmeterol, compared with 38 events in 33 patients given fluticasone only (hazard ratio 1.03 (95% confidence interval 0.64 to 1.66); non-inferiority achieved $P=0.003$).

No asthma related deaths occurred during the study, and two patients treated with fluticasone only required asthma related intubation. In terms of asthma control, the risk of a severe asthma exacerbation was 21% lower in the fluticasone-salmeterol group than in patients treated with fluticasone alone (0.79 (0.70 to 0.89)).

“It is clear that among patients with asthma who have not had life threatening episodes in the past and are highly adherent to their drug regimen, it is likely that the use of salmeterol together with fluticasone in a single inhaler is safe,” said Fernando Martinez, of the University of Arizona in Tucson, USA, in an accompanying editorial.² “For these patients and this combination, the black box warning should be lifted.”

But he warned, “What remains unanswered is whether this conclusion applies to patients who have the most severe and unstable disease.

“For these patients, the safe clinical approach is to maintain the same precautions in using fluticasone-salmeterol that have been recommended until now for all patients with asthma.”

- 1 Stempel DA, Raphiou IH, Kral KM, et al. Serious adverse events with fluticasone plus salmeterol versus fluticasone alone. *N Engl J Med* 2016; doi:10.1056/NEJMoa1511049.
- 2 Martinez FD. Safety of fluticasone plus salmeterol in asthma—reassuring data, but no final answer. *N Engl J Med* 2016; doi:10.1056/NEJMe1601040.

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